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REVIEW

Patient-specific dosimetry in peptide receptor radionuclide therapy: a clinical review

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Abstract Neuroendocrine tumours (NETs) belong to a relatively rare class of neoplasms. Nonetheless, their prevalence has increased significantly during the last decades. Peptide receptor radionuclide therapy (PRRT) is a relatively new treatment approach for inoperable or metastasised NETs. The therapeutic effect is based on the binding of radiolabelled somatostatin analogue peptides with NETs' somatostatin receptors, resulting in internal irradiation of tumours. Pre-therapeutic patient-specific dosimetry is essential to ensure that a treatment course has high levels of safety and efficacy. This paper reviews the methods applied for PRRT dosimetry, as well as the dosimetric results presented in the literature. Focus is given on data concerning the therapeutic somatostatin analogue radiopeptides ^{111}In-[DTPA^0,$_D$-Phe^1]-octreotide (^{111}In-DTPA-octreotide), ^{90}Y-[DOTA^0,Tyr^3]-octreotide (^{90}Y-DOTATOC) and ^{177}Lu-[DOTA^0,Tyr^3,Thr^8]-octreotide (^{177}Lu-DOTATATE). Following the Medical Internal Radiation Dose (MIRD) Committee formalism, dosimetric analysis demonstrates large interpatient variability in tumour and organ uptake, with kidneys and bone marrow being the critical organs. The results are dependent on the image acquisition and processing protocol, as well as the dosimetric imaging radiopharmaceutical.

Introduction

Neuroendocrine tumours (NETs) arise from cells of the diffuse endocrine system. They belong to a relatively rare class of neoplasms. Nevertheless, their prevalence has increased significantly during the last decades, mainly due to the improvement of the diagnostic procedures' efficacy and to a better knowledge of this subject. According to Surveillance, Epidemiology, and End Results (SEER) data, the age-adjusted incidence of NETs rose from 1.9 to 5.25 cases per 100,000 people between 1973 and 2004 [1]. Some of the clinical and pathologic features of these tumours are characteristic of the organ of origin [2]. Excluding small-cell lung carcinomas, the most frequent NETs occur in the digestive tract (gastroenteropancreatic NETs—GEP NETs) (66 %), followed by the rest of the respiratory tract (31 %) [3]. NETs usually over-express specific somatostatin receptors (sstr) at their cell surfaces, sstr$_{1-5}$, a characteristic which can be of great value in their localisation and treatment.

Treatment of NETs is typically multidisciplinary and should be individualised according to the tumour size, grade, location and secretory status [4]. Peptide receptor radionuclide therapy (PRRT) is a relatively new treatment approach for inoperable or metastasised NETs. It involves the systemic administration of a radiolabelled somatostatin

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analogue peptide, designed to target with high affinity and specificity somatostatin receptors over-expressed on tumours, and especially $sstr_2$ [5].

Clinical trials have shown large interpatient variability in the biodistribution and tumour uptake of the radiopharmaceutical [6–8]. This fact stimulates the need for personalised therapy planning, rather than implementing a fixed therapeutic regimen approach. Pre-therapeutic patient-specific dosimetry is the tool for a treatment course with high levels of safety and efficacy. The main goal of dosimetry is the optimisation of the therapeutic outcome by maximising the dose delivered to the tumour, while keeping the dose delivered to critical organs at acceptable levels. In most cases, the critical organs are considered to be the kidneys and the bone marrow [9–11]. Patient-specific imaging is a prerequisite for the dosimetric estimations, so as to define the tracer biodistribution in each patient. Patient imaging data are acquired from planar, SPECT or PET images after injection of the imaging radiopharmaceutical. In some cases, the exact same radiopharmaceutical is used for both imaging (diagnostic and/or dosimetric) and therapeutic purposes, an approach referred in the bibliography as "theranostics" [8, 12–14]. Image quantification and absorbed dose estimations are based on the Medical Internal Radiation Dose (MIRD) Committee formalism [15]. Specific software programmes, such as MIRDOSE, OLINDA/EXM, LundADose, and STRATOS, are an essential tool when performing dosimetric estimations in a clinical environment [16–19].

This paper reviews the methods and results of PRRT dosimetry presented in the literature, mainly for the therapeutic somatostatin analogue radiopeptides ^{111}In-[DTPA^0,$_D$-Phe^1]-octreotide (^{111}In-DTPA-octreotide), ^{90}Y-[DOTA^0,Tyr^3]- octreotide (^{90}Y-DOTATOC) and ^{177}Lu-[DOTA^0,Tyr^3,Thr^8]-octreotide (^{177}Lu-DOTATATE).

Materials and methods

Studies inclusion criteria

This review includes studies that have performed dosimetry in adult patients for the therapeutic radiopharmaceuticals ^{111}In-DTPA-octreotide, ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE. Furthermore, dosimetric studies presented here are those published the last 15 years (2000–2014), with those of ^{177}Lu-DOTATATE being published the last 5 years (2010–2014). An additional inclusion criterion was provision of dosimetric data for at least two regions of interest. Finally, this review includes data presented in the form of mGy/MBq, unless a fixed activity is administered to all patients, and in the form of a mean or a median value.

PRRT radiopharmaceuticals

Each nuclear medicine department implements its own PRRT protocol, according to which the total injected activity, the number of therapy cycles, the injected activity per cycle as well as the time interval between cycles are defined. In Table 1, some PRRT schemes, most commonly applied, are listed.

The therapeutic radiopharmaceutical consists of a radionuclide chelated to a somatostatin analogue peptide, for the purpose of delivering cytotoxic radioactivity to the tumour (Table 2). The salient features of the radiopharmaceutical which define its suitability as a PRRT radiopharmaceutical are:

- *The ligand.* It consists of the chelating agent and the somatostatin analogue peptide. The chelating agent provides the stability of the radionuclide-ligand compound. The peptide is designed to target with high-affinity cell surface somatostatin receptors ($sstr_{1–5}$), and especially $sstr_2$ that is overexpressed on NETs.
- *The radionuclide.* It is useful for its radioactive properties, namely adequate energy transfer to the tumour. The basic characteristics of radionuclides used in PRRT are presented in Table 3.
- *The activity.* The injected activity has to be carefully selected so as to cause maximum damage to tumour cells, while keeping radiation exposure to normal tissues at safe levels.

Studies with ^{111}In-DTPA-octreotide

Early studies, in the mid-to-late 1990s, investigated the safety and efficacy of using high activities of the imaging compound ^{111}In-DTPA-octreotide as a therapeutic radiopharmaceutical [12, 20]. The idea of using this compound for therapy was based on the high linear energy transfer Auger electrons emitted by ^{111}In. Despite some encouraging results in symptomatology, partial response (PR) was rarely observed (Table 4) [21]. The most common explanation for this was that the cytotoxic effect of the Auger electrons requires proximity of the ^{111}In-labelled peptide to the nucleus, due to the very short particle range of Auger electrons [22]. Furthermore, serious side effects of leukaemia and myelodysplastic syndrome (MDS) were reported in three patients receiving the highest cumulative dose (90–100 GBq) (and estimated bone marrow radiation doses of more than 3 Gy) [23]. In Europe, therapy protocols with ^{111}In-DTPA-octreotide were practically laid aside in favour of the more efficient β-emitters ^{90}Y and ^{177}Lu. Table 4 summarises the tumour response in treatment with ^{111}In-DTPA-octreotide reported in various studies.

Table 1 PRRT schemes applied by several groups

Study	Compound	No. cycles	A_{inj}/cycle	A_{total}	Time interval (weeks)
Krenning et al. [12]	^{111}In-DTPA-octreotide	8–14	6–7 GBq	Max: 74 GBq	≥2
Valkema et al. [23]		≥8	6–11 GBq	20–160 GBq	2
Waldherr et al. [24]	^{90}Y-DOTATOC	4	Escalating intravenous injections: 0.925–2.035 GBq/m^2	6 GBq/m^2	6
Waldherr et al. [25]		4	1.85 GBq	7.4 GBq/m^2	6
Bodei et al. [26]		2	Group escalating intravenous injections: 2.96–5.55 GBq	5.9–11.1 GBq	≥8
Valkema et al. [75]		≥4	Escalating intravenous injections: 0.925–3.7 GBq/m^2	1.3–24 GBq	6–9
Imhof et al. [76]		1–10	3.7 GBq/m^2	3.7–37 GBq/m^2	NS
Garkavij et al. [51]	^{177}Lu-DOTATATE	3–4	7.4 GBq	22.2–29.6 GBq	8–10
Bodei et al. [30]		Group 1			6–9
		(Median) 6	3.7–5.2 GBq	3.7–29.2 GBq	
		Group 2			
		(Median) 4	5.2–7.4 GBq	5.6–28.9 GBq	
Claringbold et al. [31]		4 (except for 8 patients)	7.8 GBq	max: 31.2 GBq	8
Sansovini et al. [32]		5	Full dosage scheme		NS
			(Mean) 3.7 GBq	11.1–19.9 GBq	
			Reduced dosage scheme		
			(Mean) 5.6 GBq	20.7–27.8 GBq	

PRRT Peptide receptor radionuclide therapy, *No* number, A_{inj} injected activity, A_{total} total cumulated activity, *DTPA* diethylenepentaacetic acid, *DOTA* 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, *[111]In- DTPA-octreotide* [^{111}In-DTPA[0],[D]-Phe[1]]octreotide, *[90]Y-DOTATOC*: [^{90}Y-DOTA,Tyr[3]]octreotide, *[177]Lu-DOTATATE*: [[177]Lu- DOTA[0],Tyr[3],Thr[8]]octreotide, *NS* not stated

Studies with ^{90}Y-DOTATOC

As ^{111}In-DTPA-octreotide turned out to be ineffective for PRRT, researchers focused on the use of high-energy β-emitters, such as [90]Y. [90]Y is a nearly pure β-emitting radionuclide with a physical half-life of 64 h. The high-energy electrons (maximum energy 2.28 MeV) and maximum tissue penetration range of ∼11 mm (Table 3), make ^{90}Y more suitable for tumour cell killing, compared to ^{111}In, also taking into consideration the cross-fire effect. Among other ^{90}Y labelled peptides (such as ^{90}Y-DOTA-TATE and ^{90}Y-lanreotide), ^{90}Y-DOTATOC is the most commonly used in PRRT [24–27]. The overall response rate (complete, partial and minor response—CR, PR and MR) reported in studies with ^{90}Y-DOTATOC, fell in the range of 19–36 %, while the majority of patients showed disease stabilisation (5.2–69 %) (Table 4). In PRRT with ^{90}Y-DOTATOC, kidneys are the dose-limiting organs, but also liver toxicity can be reported. In order to reduce the high kidney irradiation, positively charged amino acids were coinfused to competitively inhibit the proximal tubular reabsorption of the radiolabelled peptide. The coadministration of these amino acids led to a significant reduction in the renal absorbed dose. Specifically, in a study by de Jong et al., the renal absorbed dose was reduced by a mean of 27 % (range: 9–53 %) [28].

Studies with ^{177}Lu-DOTATATE

[177]Lu emits both β- and γ- radiation, allowing post-treatment imaging and dosimetry assessments. Compared to ^{90}Y, it has a lower tissue penetration range (R_{max} ∼ 2 - mm), indicating that most of the energy is absorbed in small volumes. Some physical properties of ^{177}Lu are listed on Table 3. The first treatment effects of ^{177}Lu-DOTA-TATE were published in 2003 for 35 patients who had GEP NETs [29]. Since then, several centres worldwide conducted clinical trials with ^{177}Lu-DOTATATE [30–32]. The reported overall response rates were higher when compared to ^{90}Y-DOTATOC (Table 4). Serious side effects in patients treated with ^{177}Lu-DOTATATE included renal toxicity (creatinine clearance loss of about 3.8 %

per year), acute bone marrow toxicity (grade 3 and 4), mostly reversible (in 2–3 % of treatment cycles) and liver toxicity [5, 33].

Table 2 Imaging radiopharmaceuticals used in PRRT and imaging technique applied for both diagnostic and dosimetric purposes

Radionuclide	Ligand (chelator-peptide)	Imaging modality	Image acquisition	Used for therapy[a]
[111]In	DTPA-octreotide	γ-Camera	CV: Planar, WB/SPECT	✔
	DOTA-TOC			✗
[86]Y	DOTA-TOC	PET	2D Mode/ 3D mode	✗
[177]Lu	DOTA-TATE	γ-Camera	CV: Planar, WB/SPECT	✔
[68]Ga	DOTA-TOC	PET	2D Mode/ 3D mode	✗
[99m]Tc	HYNIC-TOC	γ-Camera	CV: Planar, WB/SPECT	✗

In the last column those which are also used for therapy are listed

DTPA diethylenepentaacetic acid, *DOTA* 1,4,7,10-tetraazacyclodo decane-1,4,7,10-tetraacetic acid, *HYNIC-TOC* [HYdrazinoNICotinyl-Tyr^3]octreotide, *DTPA-octreotide* [DTPA^0,$_D$-Phe^1]octreotide, *DOTA-TOC* [DOTA,Tyr^3]octreotide, *DOTATATE* [DOTA^0,Tyr^3,Thr^8]octre-otide, *CV* conjugate view method, *WB* whole-body

[a] Another important PRRT therapeutic radiopharmaceutical not mentioned in the Table is ^{90}Y-DOTATOC. ^{90}Y-DOTATOC brems-strahlung imaging can be utilised for dosimetric purposes, but not for diagnosis

Dosimetric imaging radiopharmaceuticals

Scintigraphy with radiolabelled somatostatin analogue peptides has become one of the most important imaging procedures for the diagnosis, staging and localisation of somatostatin receptor-positive tumours. It is also important for selecting patients with inoperable and/or metastatic tumours for subsequent PRRT. Furthermore, patient imaging is the prerequisite process for dosimetric assessment.

The imaging radiopharmaceutical may be the same or differ from the therapeutic one. Its selection is based on the following criteria:

- *The ligand.* Ideally, the ligand of both imaging and therapeutic radiopharmaceutical should be the same. If this is not feasible, they should be chemically analo-gous, in order to eliminate the differences in the radiopharmaceutical biodistribution.
- *The radionuclide.* The type of radiation emitted should enable imaging and its physical half-life should permit assessment of the radiopharmaceutical biokinetics in a short period of time.
- *The activity.* In case that different radiopharmaceuticals are used the injected activity of the imaging radiophar-maceutical should be considerably lower than the therapeutic one, in order to keep patient radiation exposure to low levels.

In the dosimetric imaging procedure the renal protection regimen applied should be the same as the therapeutic one, since the amino acid infusion affects the degree of activity

Table 3 Physical properties of radionuclides used in PRRT

Radio-nuclide	$T_{1/2\ phys}$ (days)	Type of radiation emitted	Energy (MeV)/ abundance (%)	Particle range in tissue (mm)	Application
[111]In	2.83	γ	γ: 0.173 (87 %), 0.247 (94 %)	–	Imaging, therapy
		e-Auger	e-Auger: 0.005–0.025	$R_{max\ (e-\ Auger)}$: 0.20–0.55	
		e-IC	e-IC: 0.144–0.245		
[90]Y	2.67	β$^-$	β$_{max}$: 2.28 (99.9 %)	R_{max}: 11.3 R_{mean}: 4.1	Therapy
		β$^+$	β$_{max}^+$: 1.70 (0.003 %)		Imaging[a]
[86]Y	0.6	β$^+$	β$_{max}^+$: 1.20 (33 %)	R_{mean}: 2	Imaging
[177]Lu	6.73	β$^-$ and γ	β$_{max}$: 0.498 (79 %)	R_{max}: 2 R_{mean}: 0.5	Imaging, therapy
			γ: 0.113 (6.5 %), 0.208 (11 %)	–	
[68]Ga	0.047	β$^+$	β$_{max}^+$: 1.92 (89 %)	R_{max}: 9 R_{mean}: 1	Imaging
[99m]Tc	0.25	γ	0.141 (89.1 %) 0.0184 (4.0 %) 0.0183 (2.1 %)	–	Imaging

PRRT Peptide receptor radionuclide therapy, $T_{1/2\ phys}$ physical half-life, *IC* internal conversion

[a] The imaging property of ^{90}Y with PET has been so far implemented in selective internal radiation therapy of the liver

Table 4 Tumour responses in patients with neuroendocrine tumours, treated with different radiolabelled somatostatin analogues

Study	Compound	No. patients	Tumour response[a]				
			CR	PR	MR	SD	PD
Krenning et al. [12]	^{111}In-DTPA-octreotide	30	0 (0 %)	6 (20 %)[b]		8 (27 %)	16 (53 %)
Valkema et al. [23]		40	0 (0 %)	1 (2.5 %)	6 (15 %)	14 (35 %)	19 (48 %)
Waldherr et al. [24]	^{90}Y-DOTATOC	41	1 (2 %)	9 (22 %)	5 (12 %)	20 (49 %)	6 (15 %)
Waldherr et al. [25]		39	2 (5 %)	7 (18 %)	NS	27 (69 %)	3 (8 %)
Bodei et al. [26]		40[c]	1 (2.6 %)	7 (18 %)	NS	18 (46 %)	13 (33 %)
Valkema et al. [75]		58	0 (0 %)	5 (9 %)	7 (12 %)	29 (50 %)	17 (29 %)
Imhof et al. [76]		1109[d]	7 (0.6 %)	378 (34.1 %)[b]		58 (5.2 %)	438 (39.5 %)
Garkavij et al. [51]	^{177}Lu-DOTATATE	12	0 (0 %)	2 (17 %)	3 (25 %)	5 (42 %)	2 (17 %)
Bodei et al. [30]		51	1 (2 %)	14 (27 %)	13 (26 %)	14 (27 %)	9 (18 %)
Claringbold et al. [31]		33	0 (0 %)	8 (24 %)	NS	23 (70 %)	2 (6 %)
Sansovini et al. [32]		52	6 (12 %)	14 (27 %)	NS	24 (46 %)	8 (15 %)

No Number, *CR* complete response, *PR* partial response, *MR* minor response, *SD* stable disease, *PD* progressive disease, *NS* not stated

[a] Values indicate number of patients and the corresponding percentages

[b] No distinction between PR and MR

[c] One patient was stated as not evaluated

[d] Patients not mentioned are those with other type of response, such as biochemical or mixed response

reabsorption in the proximal tubules. If dosimetric imaging is performed without amino acid coinfusion, the renal radiation doses are overestimated [34]. This overestimation is independent of the radionuclide used; however, attention should be paid to the imaging ligand, which should retain the chemical structure of the therapeutic one, so that the dosimetric procedure simulates the therapeutic one effectively.

Table 2 summarises the NETs imaging radiopharmaceuticals most often used, as well as the imaging technique used with each one.

Imaging with [111]In

^{111}In-DTPA-octreotide has been used for almost 20 years for the diagnosis and staging of somatostatin receptor-positive tumours and became the gold standard for the detection of NETs. [111]In facilitates dosimetry assessments due to its γ-ray emission. Thereafter, it has been used as a surrogate for ^{90}Y-DOTATOC, as the quantification of ^{90}Y bremsstrahlung images was rather difficult. However, it was not the first choice for simulating ^{90}Y-DOTATOC biokinetics because of the difference in the chemical nature of the ligands. In order to maintain similar chemical and kinetic behaviour, the use of ^{111}In-DOTATOC has been investigated in several studies [35–37].

Compared to ^{111}In-DTPA-octreotide, ^{111}In-DOTATOC exhibited similar distribution and excretion patterns. However, the uptake in somatostatin receptor-positive organs and most tumours was higher for [111]In –DOTATOC.

Imaging with [86]Y

Another alternative for ^{90}Y-DOTATOC image quantification, but a far more demanding solution from a technical and financial point of view, was to use DOTATOC labelled with the positron emitter [86]Y. The major advantage of [86]Y-DOTATOC is that it totally preserves the chemical structure of ^{90}Y-DOTATOC. Therefore, it is generally considered as the gold standard for simulating ^{90}Y-DOTATOC biokinetics. Additionally, PET offers improved accuracy and spatial resolution. Nevertheless, the low positron abundance (33 %), the emission of multiple, high-energy γ-rays, the high production cost and the low availability of [86]Y were inhibiting factors in the routine utilisation of this compound [38]. In a comparison of [86]Y-DOTATOC to ^{111}In-DTPA-octreotide, the reported results indicated that the biokinetics of these two compounds were relatively similar in the organs but differed in the uptake pattern of the metastases. Particularly, [86]Y-DOTATOC showed much higher uptake and slower washout in tumours [39].

Imaging with [177]Lu

If PRRT is performed with ^{177}Lu, its γ-ray emission enables dosimetry and therapy with the same compound. Therefore dosimetry is usually performed during PRRT, following the injection of ^{177}Lu-DOTATATE. This approach eliminates the uncertainties occurring from the use of different compounds, due to the difference in biokinetics. Nevertheless, due to [177]Lu's long physical half-life of 6.7 days, a long

time interval is required between the time of administration and acquiring the last dosimetric image acquisition. Ideally this should be more than 1 week [15]. Thus, patient discomfort could be pointed out as one of ^{177}Lu imaging drawbacks.

Imaging with ^{68}Ga

A further important step in the diagnosis of NETs was the introduction of somatostatin-based PET tracers labelled with the generator-produced radiometal ^{68}Ga. The somatostatin analogue peptides clinically used are based on the three octapeptides [Tyr^3]octreotide (TOC), [Tyr^3,-Thr^8]octreotide (TATE) and [1-Nal^3]octreotide (NOC), conjugated to DOTA. These somatostatin analogues showed high affinity for certain sstr. Additionally, since ^{68}Ga is a generator product, rather than a cyclotron-produced product, a relatively simple labelling can be performed on an everyday basis [21]. In addition to these advantages, ^{68}Ga peptides seem desirable for dosimetry, as they preserve the same chemical ligand structure with that of the therapeutic compound. Nonetheless, they are not suitable for accurate dosimetric calculations, mainly due to the very short physical half-life of ^{68}Ga (68 min). Taking into account that the effective half-life is even shorter than the physical one, for accurate determination of time–activity curve, PET scans with ^{68}Ga should last just a few minutes, in accordance to MIRD guidelines [15]. This would result in poor statistics and ineffective subsequent dosimetric evaluations.

Imaging with ^{99m}Tc

Clinical studies with ^{99m}Tc-somatostatin analogue peptides began in the late 1990s [40]. At present, ^{99m}Tc-ethylenediamine-N,N9-diacetic acid (EDDA)/HYNIC,Tyr3]octreotide (^{99m}Tc-HYNIC-TOC) is available in different European countries and its use in clinical practice for the diagnosis of NETs is gradually gaining acceptance. Among other advantages, its availability, its physical properties (γ-emitter, $T_{1/2\ physical} = 6$ h) and the peptide –TOC, same as that with the therapeutic compound ^{90}Y-DOTATOC, made it one of the principal choices for NETs imaging and dosimetry. ^{99m}Tc-HYNIC-TATE has also been used by some groups. Hubalewska et al. demonstrated superior image quality of ^{99m}Tc-HYNIC-TATE over ^{111}In-DTPA-octreotide in 75 patients [41]. Cwikla et al. compared the 2 compounds ^{99m}Tc-HYNIC-TOC and ^{99m}Tc-HYNIC-TATE in the same 12 patients and concluded that both give excellent high-quality images. A similar number of metastatic sites could be seen with both agents, though ^{99m}Tc-HYNIC-TATE may have some advantage in lymph node and liver metastases [42].

Dosimetry

Patient-specific dosimetry can provide information on organs and NETs radiation absorbed doses and assess the risk of critical organ toxicity (kidneys, bone marrow). Different dosimetry methods can be applied, with various levels of complexity, depending on study objective, human and software resources, as well as workflow practical factors. All dosimetry methods require input data to be derived from patient-specific scintigraphic images and, when needed, from biological samples, such as blood and urine. Patient imaging can be performed with whole-body scans, or with SPECT. Planar and SPECT dosimetry gave comparable results in areas free of tumours. However, in tumour dosimetry, or in the case of overlapping organs, SPECT dosimetry was more accurate, although more time-demanding [11].

Since gamma camera systems provide the imaging data in counts or count rates, a mathematical model should be applied to convert counts to activity values [15]. For accurate image quantification several correction factors should be taken into account, including photon attenuation in the patient's body, scatter, background activity, dead-time, source self-absorption, partial volume effects for small objects, collimator effects and proper calibration of the imaging system. Some of these factors are obtained from patient images (attenuation correction, scatter, background activity subtraction, source self-absorption) while others from experimental measurements. The determination of all these correction factors can be a painstaking process, and it is at the discretion of each dosimetry team which method of quantification should be applied.

Once the organ activity values are estimated, they are then converted to absorbed dose values. Dosimetric analysis is generally based on MIRD Committee schema [15]. The absorbed dose is estimated from the organ uptake and retention of administered radiopharmaceutical. In order to attain the therapeutic radiopharmaceutical biodistribution, simulation with an appropriate imaging radiopharmaceutical is being performed. The basic dosimetry equations, according to MIRD schema, are the following:

$$\overline{D}_{target} = \sum_{sources} \tilde{A}_{source} \cdot S_{target \leftarrow source} \tag{1}$$

$$\tau_{source} = \tilde{A}_{source}/A_0 \tag{2}$$

$$\overline{D}_{target} = A_0 \sum_{sources} \tau_{source} \cdot S_{target \leftarrow source} \tag{3}$$

where $\overline{D}_{target}$ is the mean target absorbed dose (Gy or rad), $\tilde{A}_{source}$ is the source cumulated activity (Bq·sec or µCi·hr), $S_{target \leftarrow source}$ is the mean absorbed dose per unit cumulated activity (Gy/Bq·sec or rad/µCi·hr), τ_{source} is the source region residence time (sec or hr), A_0 is the administered

activity (Bq or μCi). From Eq. 1 and 3 it can be seen that the target absorbed dose depends on two main parameters:

(i) Time-independent physical factors: the so-called S-factors, which include characteristics of type and energies of the radiations emitted, geometrical and composition aspects of the source, target and intervening media. The S-factors have been tabulated by MIRD in 1975 and 1978 [43, 44], and followed other relevant publications [45, 46].

(ii) Time-dependent biokinetic factors: incorporated within $\tilde{A}$ or τ.

Sequential imaging as a function of time postadministration of the radiopharmaceutical provides the time–activity curve for each source region. The area under the curve defines the cumulated activity, $\tilde{A}$. It should be noted that selection of adequate time points, appropriately time-distributed, for sampling radiopharmaceutical biokinetics has a significant effect on the resulting time–activity curve and conclusively on the precision of estimated target absorbed dose.

Data processing for absorbed dose estimations can be performed by computer software packages. There are several codes/programmes available now, varying from the most simple to the most complex; the latter being designed to apply patient-specific adjustments. Some examples of such programmes are MIRDOSE, OLINDA/EXM, LundADose, STRATOS [16–19]. The key features of these programmes differ significantly and the selection of the appropriate programme depends on the financial and computational cost as well as the dosimetric level accuracy desired. Some are based on standard mathematical phantoms and are simple and fast, while others are highly accurate, because they take the individualized patient anatomy into account, but they are time consuming.

Table 5 summarises the basic dosimetric protocols features for data acquisition and processing applied by several groups. It should be mentioned that in most cases of planar image acquisition, an additional SPECT scan was acquired for improved accuracy in organ depth determination.

Results

Table 6 presents the dosimetric results for organs and tumours, published by the studies mentioned in Table 5.

Discussion

Results analysis

Due to large interpatient variability in tumour and organ uptake, accurate and reliable dosimetric estimations are needed to fully exploit the therapeutic potential of PRRT. In this way, the dose delivered to tumours is maximised, while the dose delivered to critical organs remains at acceptable levels. Nonetheless, and to the best of our knowledge, dosimetry is systematically implemented in a relatively limited number of nuclear medicine centres worldwide. This is mainly due to the time-consuming methods that are required for reliable dosimetry. Dosimetric procedures are demanding with respect to the patients' discomfort, the level of staff commitment and available facilities. In most cases, after the patients are discharged, they should return to the Nuclear Medicine Department for the completion of image acquisition, which takes at least 2 days. Furthermore, reaching an adequate dosimetric outcome requires the collaboration of a multi-disciplinary team, including medical physicists, nuclear medicine physicians, oncologists and technologists. If any link of this chain is reluctant to cooperate, dosimetric procedures become difficult to implement. Additionally, for accurate dosimetric estimations the department should be equipped with appropriate software programmes, imaging or/and counting systems and phantoms.

These difficulties raised objections as to whether dosimetry-based radionuclide therapy is worth the extra effort over fixed-dose therapies. The benefit of dosimetry-based radionuclide therapy over fixed dose therapy remains to be proven by randomised phase III clinical trials. Nevertheless, studies that provide initial evidence supporting further consideration of individualised therapy planning have been published. In a study of Stabin [47] the objections to dosimetry-based approach were addressed and the conclusion of the analysis was that careful use of patient-specific dosimetry should become routine practice. Furthermore, several investigators have shown that patient-specific dosimetry can produce strong correlations between absorbed dose, or biologically effective dose (BED), and observed effects in tumours and normal organs. Shen et al. [48] using a ^{90}Y-antibody in radioimmunotherapy, found a strong correlation between bone marrow dose and observed marrow toxicity, whereas Pauwels et al. [34] correlated tumour absorbed dose with tumour reduction in their study with ^{90}Y-DOTATOC. Taking radiobiological models into account, Barone [6] proved that BED is a reliable predictor of renal toxicity. The inclusion of the most advanced techniques in the dosimetric procedure, some of them being realistic body morphometry, radiobiological models, 3D voxel-by-voxel dosimetry, can produce accurate dose evaluations, which can subsequently be used for individual therapy planning.

In the Euratom Directives of 1997, it is stated that "for all medical exposures of individuals for radiotherapeutic purposes, exposures of target volumes shall be individually planned, taking into account that doses of non-target

Table 5 Basic parameters of PRRT dosimetric protocols for data acquisition and processing, applied by several groups

PRRT r/p[a]	Study	No. patients	Dosimetric imaging r/p	Image acquisition	Dosimetry software
[111]In	(In-1) Kontogeorgakos et al. [77]	12	^{111}In-DTPA-octreotide	γ-Camera CV Method, Blood + urine samples: γ-counter	Monte Carlo MCNP-4C code
	(In-2) Barone et al. [55]	6		SPECT Scans Blood + urine samples: γ-counter	MIRDOSE 3.1
[90]Y	(Y-1) Förster et al. [39]	3	^{111}In-DTPA-octreotide	γ-Camera CV Method, Blood + urine samples: γ-counter	MIRDOSE 3.1
		3	[86]Y-DOTATOC	PET 2D Mode, Blood + urine samples: γ-counter	MIRDOSE 3.1
	(Y-2) Chinol et al. [78]	18	^{111}In-DTPA-octreotide	γ-Camera WB and SPECT scans	NS
	(Y-3) Jamar et al. [7]	24	[86]Y-DOTATOC	PET 2D Mode, Blood + urine samples: γ-counter	MIRD programme 3.0
	(Y-4) Bodei et al. [26]	6	^{111}In-DOTATOC	γ-Camera WB Scans Blood + urine samples	NS
	(Y-5) Helisch et al. [50]	8	^{111}In-DTPA-octreotide	γ-Camera CV Method, Blood + urine samples: γ-counter	MIRDOSE 3.1
		8	[86]Y-DOTATOC	PET 2D Mode, Blood + urine samples: γ-counter	MIRDOSE 3.1
	(Y-6) Forrer et al. [37]	5	^{111}In-DOTATOC	γ-Camera CV Method, Blood + urine samples: γ-counter	MIRDOSE 3.1
	(Y-7) Rodrigues et al. [79]	45	^{111}In-DOTATOC	γ-Camera CV Method, Blood + urine samples: γ-counter	NS
	(Y-8) Hindorf et al. [80]	30	^{111}In-DOTATOC	WB: Geiger counter, SPECT	NS
	(Y-9) Barone et al. [55]	6	[86]Y-DOTATOC	PET 2D Mode, Blood + urine samples: γ-counter	MIRDOSE 3.1
	(Y-10) Grassi et al. [81]	17	^{111}In-DOTATOC	γ-Camera WB Scans	ULMDOS and OLINDA/EXM

Table 5 continued

PRRT r/p[a]	Study	No. patients	Dosimetric imaging r/p	Image acquisition	Dosimetry software
[177]Lu	(Lu-1)	24	^{177}Lu-DOTATATE	γ-Camera	OLINDA
	Sandström et al. [11]			Planar CV method & SPECT	
	(Lu-2)	21		γ-Camera	NS
	Garkavij et al. [51]			Planar CV method & SPECT	
	(Lu-3)	12		NS	NS
	Bodei et al. [30]				
	(Lu-4)	33		γ-Camera	Monte Carlo MCNPX code
	Claringbold et al. [31]			WB and SPECT scans	
	(Lu-5)	200		γ-Camera	OLINDA/EXM
	Sandström et al. [82]			planar CV method & SPECT,	
				Blood + urine samples: well counter	
	(Lu-6)	61		γ-Camera	OLINDA/EXM 1.0
	Gupta et al. [83]			CV Method	
	(Lu-7)	185		γ-Camera	OLINDA/EXM
	Schuchardt et al. [84]			CV Method	

The first column indicates the therapeutic radiopharmaceutical studied by each subgroup

PRRT Peptide receptor radionuclide therapy, *r/p* radiopharmaceutical, *No* number, *WB* whole-body, *NS* not stated, *CV* conjugate view method, *DTPA* diethylenepentaacetic acid, *DOTA* 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, *[111]In- DTPA-octreotide* [^{111}In-DTPA[0],[D]-Phe[1]]octreotide, *[90]Y-DOTATOC* [^{90}Y-DOTA,Tyr[3]]octreotide, *[177]Lu-DOTATATE* [[177]Lu- DOTA[0],Tyr[3],Thr[8]]octreotide

[a] Studies are divided into three subgroups; the first subgroup has worked with the therapeutic radiopharmaceutical ^{111}In-DTPA-octreotide, the second with ^{90}Y-DOTATOC, while the third with ^{177}Lu-DOTATATE

volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure" [49]. These Directives form an additional stimulus for dosimetry. However, the fact that dosimetry is still not widely performed stresses the need for sufficient education of personnel and further development of dosimetric conscience.

Four parameters that significantly affect the dosimetric outcome are the selected dosimetric imaging radiopharmaceutical, the image acquisition method, the accuracy of activity quantification, as well as the temporal sampling.

For dosimetry of ^{90}Y-DOTATOC, the chemically analogous [86]Y-DOTATOC is generally considered as the gold standard. However, its already mentioned disadvantages in combination with the acceptable dosimetric results of ^{111}In-DTPA-octreotide have laid the use of the PET tracer aside. As depicted by Table 6, both studies comparing the biokinetics of ^{111}In-DTPA-octreotide versus [86]Y-DOTATOC in the same patients have yielded similar organ uptake, while tumour uptake seems to be underestimated if ^{111}In-DTPA-octreotide is selected, according to the studies of Förster et al. [39, 50]. In the case of ^{177}Lu-DOTATATE the exact same radiopharmaceutical is used for both dosimetric imaging and therapeutic purposes.

As far as the image acquisition method is concerned, large differences can be obtained in the estimated absorbed dose values, depending on whether planar or SPECT dosimetry is used. Studies revealed that they provide comparable results in areas free of tumours, but planar dosimetry highly overestimated the absorbed dose in organs with tumours or in overlapping organs (Table 6) [11, 51]. Despite the improved accuracy of SPECT dosimetry, many dosimetry approaches are still based on 2D scintigraphic images. This is due to the much higher demands of SPECT in terms of imaging time and data post-processing. Another application of whole-body imaging by planar scintigraphy is bone marrow dosimetry. The activity in the whole-body from serial whole-body scans should be assessed to determine the cross-absorbed dose to the bone marrow, according to EANM Dosimetry Committee guidelines [52].

The fact that imaging systems measure counts and not activity is directly related to the need for absolute quantification, equipment calibration and inclusion of necessary corrections. The correction factors, mentioned in the dosimetry section, should be included in the dosimetric protocol as patient image acquisition differs by far from the ideal imaging conditions, due to broad-beam geometry

Table 6 Dosimetric results for [111]In- DTPA-octreotide, ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE, published from the studies listed on Table 5

Study	Absorbed doses per unit administered activity (mGy/MBq)[a]				
	Kidneys	Red marrow	Liver	Spleen	Tumours
In-1 [77]	0.41 ± 0.08	$(3.5 \pm 0.8) \times 10^{-3}$	0.14 ± 0.04	1.4 ± 0.6	10.8 ± 5.4
In-2 [55]	0.2	0.05[b]	–	–	0.1*
Y-1 [39]	3.013 ± 0.805[c]	0.042 ± 0.008	0.594 ± 0.148	2.786 ± 1.535	3.73
	2.728 ± 1.408[d]	0.049 ± 0.002	0.656 ± 0.148	2.32 ± 1.97	9.87
Y-2 [78]	3.3 ± 2.2	0.03 ± 0.01	0.7 ± 0.6	7.6 ± 6.3	10.1
Y-3 [7]	3.3 ± 1.3[e]	–	–	–	2.1 ± 0.7
Y-4 [26]	3.4 ± 0.8[f]	–	0.8 ± 0.8	4.0 ± 1.6	–
Y-5 [50]	1.98 ± 0.75[c]	0.06 ± 0.03	0.4 ± 0.26	3.31 ± 1.2	9.42 ± 5.63
	1.71 ± 0.89[d]	0.06 ± 0.02	0.72 ± 0.4	2.19 ± 1.11	8.97 ± 6.55
Y-6 [37]	2.84 ± 0.64	0.17 ± 0.02	0.92 ± 0.35	6.57 ± 5.25	16.01 ± 14.64
Y-7 [79]	2.44	0.09	0.86	4.74	10.03
Y-8 [80]	LK: 3.7*	–	–	–	3.8*
	RK: 4.3*				
Y-9 [55]	2.0	0.15[b]	–	–	2.4*
Y-10 [81]	6.76	0.17	2.66	9.45	–
Lu-1 g [11]	*(planar)*	–	*(planar)*	*(planar)*	–
	RK: 0.91 ± 0.48		0.59 ± 0.43	0.77 ± 0.44	
	LK: 1.05 ± 0.92				
	(SPECT-sm.VOI)	–	*(SPECT-sm.VOIs)*	*(SPECT-sm.VOIs)*	–
	RK: 0.72 ± 0.31		0.41 ± 0.25	0.77 ± 0.36	
	LK: 0.59 ± 0.17				
Lu-2 h [51]	*(planar-method 1B)* 1.15 ± 0.29	–	–	–	–
	(SPECT-method 3) 0.90 ± 0.21	–	–	–	*(SPECT-method 3)*
					6.7*
Lu-3 [30]	0.68	0.03	0.25	0.65	0.56–56.4[i]
Lu-4 [31]	0.31*		0.62*		
Lu-5 [82]	RK: 0.62*	0.016*	0.29*	0.68*	–
	LK: 0.59*				
Lu-6 [83]	0.57 ± 0.09	–	0.27 ± 0.05	1.17 ± 0.14	3.41 ± 0.68
Lu-7 [84]	0.8*	–	–	1.1*	5.2*

LK Left kidney, *RK* right kidney, *NA* not available, *sm. VOI* small volume of interest

[a] The results are given in the form of mean value $\pm$ 1SD, mean value or median value (denoted by asterisk)

[b] Absorbed doses to red marrow estimated from direct measurements of uptake

[c] Dosimetric imaging with the radiopharmaceutical ^{111}In-DTPA-octreotide

[d] Dosimetric imaging with the radiopharmaceutical [86]Y-DOTATOC

[e] With infusion of amino-acids over 4-h

[f] With infusion of amino-acids

[g] The study has published dosimetric results obtained by three different methods. The results presented are those obtained by planar imaging and by SPECT based on small VOIs analysis. Small VOIs method results are presented as this analysis proved to be more reliable than whole-organ dosimetry

[h] The absorbed dose to the kidneys was evaluated using three different quantification methods. The results presented are those obtained by the planar activity imaging (method 1B) and by SPECT imaging (method 3). Method 1B was the one used for therapy. Method 3 results are presented as analysis was based only on SPECT activity images

[i] Tumour absorbed dose is given in the form of range, since mean or median values are not available

conditions. The dosimetry team can face a number of difficulties in determining the correction factors, the most important of them being the time and skills needed, as well as the equipment availability for the experimental set-ups. Although being a time- and labour-intensive process, attention to determining these factors influences the accuracy of image quantification and hence the accuracy of the dosimetric results.

Furthermore, selection of image acquisition time points can have a significant effect on dosimetric estimation accuracy. For an appropriate temporal sampling, a minimum of three sampling points, near the effective half-life T_{eff}, ~ 3 T_{eff} and ~ 5 T_{eff}, should be chosen for the uptake and washout phases, according to MIRD guidelines [15]. Inappropriate temporal sampling and data interpolation methods could lead to errors in absorbed dose estimation even greater than 20 %. For DOTATOC and DOTATATE peptides, whose time–activity curve generally comprises two kinetic phases, uptake and washout, at least six time points are needed. As each experimental point requires time-consuming acquisitions, the whole process would be demanding for patients, clinicians and personnel. In this respect, finding a compromise that balances accuracy and feasibility seems to be an optimal approach for clinical studies. Generally, radionuclides with relatively short physical half-lives, i.e., of a few hours, such as ^{99m}Tc ($T_{1/2\ physical}$ = 6 h), should be preferred for dosimetric imaging rather than long- lived, i.e., $T_{1/2\ physical} \sim$ days, such as ^{111}In (2.8 days), or very short-lived radionuclides, i.e., $T_{1/2\ physical} \sim$ minutes, such as ^{68}Ga (68 min). Dosimetric imaging with long-lived radionuclides is impractical for reasons of patients inconvenience, since the last scan should be acquired at $\sim 5T_{eff}$, and radiation safety issues. Additionally, very short-lived radionuclides are impractical for dosimetric imaging, since the rapid activity falloff requires a very short scan duration, resulting in poor statistics.

Dosimetry software programmes can facilitate the dosimetric procedure in a busy clinical environment. Until the early 2000s the main dosimetric tool available was MIRDOSE3 software [16]. Using tabulated specific absorbed fractions (SAFs), radionuclide decay data and specific anthropomorphic models, the main function of this programme is to provide estimates of the mean radiation dose per unit administered activity, given the source organ residence times [53]. The software code OLINDA/EXM was designed as an update to MIRDOSE3 [17]. The updates include decay data for more than 800 radionuclides, including selected α-emitters, new absorbed fractions in the sphere model of MIRDOSE3.1 and the ability to modify organ masses to patient-specific mass values. The limitations of MIRDOSE and OLINDA/EXM, namely calculation only of self-dose for tumours, using a sphere

model of tumours with a uniform activity distribution and the use of standard anatomic models, led to the development of more sophisticated programmes. Sjögreen and Ljungberg developed LundADose, which is used for dosimetry in clinical studies of ^{177}Lu-DOTATATE and ^{90}Y/^{111}In labelled Ibritumomab Tiuxetan [18, 54]. For SPECT/CT dosimetry, a voxel-based Monte Carlo programme is used, while in planar dosimetry corrections for attenuation, scatter, and overlapping organs are applied. Furthermore, the programme offers the possibility calculating the BED. Further research in that field led to the release of more advanced software packages, like STRATOS, by Philips [19]. The STRATOS Dosimetry Solution performs 3D voxelised dose calculations using SPECT/CT and also PET/CT data, or even using planar images as input. It performs patient-specific dose calculations based on the dose point kernel (DPK) method. The key features of the STRATOS software include registration, segmentation and visualisation of 3D images, more supported therapy radionuclides, calculation of residence-time maps, energy–dose distributions and dose–volume–histograms per region. This gradual development of more realistic programmes, which are easily adopted in everyday clinical routine and are financially affordable, is expected to contribute to the inclusion of dosimetry in radionuclide therapies, in accordance with external beam radiation therapy practice.

In PRRT, the kidneys together with the bone marrow are the dose-limiting organs at the usual administered activities. Proper kidney protection by the coinfusion of amino acid solutions enlarges the safety margin for administrating higher activities, enabling higher tumour radiation doses to be attained safely. The dosimetric results of Table 6 demonstrate that ^{90}Y-DOTATOC kidney absorbed doses are higher than these obtained with ^{177}Lu-DOTATATE. Consequently, ^{177}Lu-labelled somatostatin analogues are likely to have higher renal toxicity thresholds than ^{90}Y. Indeed, the PRRT schemes listed on Table 3 apply higher ^{177}Lu injected activities than with ^{90}Y. Thus, ^{177}Lu-labelled peptides are considered a safer option in patients with reduced renal function or when designing a retreatment regimen.

The dosimetric results of the Barone 2008 study, presented in Table 6, pointed out the higher tumour uptake of the β-emitter, ^{90}Y compared to ^{111}In [55]. These data in combination with the low tumour response (<20 %, Table 4) proved the inappropriateness of ^{111}In-labelled peptides for therapy, despite some encouraging preliminary results. Additionally, when comparing the radioisotopes used today in PRRT, ^{90}Y and ^{177}Lu, from data listed in Table 4, it can be seen that ^{177}Lu led to higher corresponding tumour responses. Concluding, the optimal treatment regimen applied, namely administration of ^{90}Y-

or ^{177}Lu-labelled peptides, or even a combination of them, is dependent on many parameters. The most important of them include the tumour size and location, the extent of disease and the patient's clinical condition.

Improvements under development

The establishment of the optimal therapeutic and dosimetric protocol for PRRT is still a matter of research. Future steps for the improvement of PRRT dosimetry focus on three main aspects: development of efficient Neuroendocrine tumour imaging radiopharmaceuticals, proper selection of therapeutic schemes and better understanding of dosimetric procedures' mathematical formalism and technical implementation.

Concerning Neuroendocrine tumour imaging, the relatively new compound ^{99m}Tc-HYNIC-TOC is a promising radiopharmaceutical. It binds to somatostatin receptors with high affinity (particularly subtype two and, to a lesser extent, subtypes three and five) and its use in clinical practice for the diagnosis of NETs is gradually gaining acceptance [42, 56]. In addition to its diagnostic value, ^{99m}Tc-HYNIC-TOC seems to be ideal for dosimetry assessments. Its physical properties (γ-emitter with a relatively short half-life of 6 h), allow the patient dosimetric imaging to be performed within no longer than 2 days. This is of great importance when considering the daily clinical schedule, the personnel burden and the patients' comfort. The compound availability should also be included in its advantages. Furthermore, when dosimetric evaluations for the therapeutic radiopharmaceutical ^{90}Y-DOTATOC are acquired, both the therapeutic and the imaging compound have the same peptide (-TOC), allowing similar biodistribution. Dosimetric data of ^{99m}Tc-HYNIC-TOC have been published by some groups [57–59].

In the search of methods for improving PRRT efficacy, studies lean towards combination therapy protocols. PRRT is commonly performed with a single radiopharmaceutical administration. The currently used therapeutic radionuclides ^{90}Y and ^{177}Lu differ markedly in their physical properties, including half-life, range and energy of emitted β-particles. Potential advantages of ^{177}Lu for PRRT include a longer half-life and β-particle ranges suitable for small tumours. By contrast, ^{90}Y emits β-particles with longer range and higher energies and therefore may be preferable for patients with bulk disease. These different characteristics led to the first clinical study of combination therapy in animals bearing tumours of various sizes [60]. Reports of clinical applications in humans, incorporating both ^{90}Y- and ^{177}Lu- labelled peptides, were published recently and indicated longer overall survival [61, 62]. Nonetheless, larger randomised trials are essential in order

to confirm these results and optimise the combination treatment protocol.

In order to improve the accuracy of absorbed dose estimates, efforts have been directed towards more sophisticated dosimetry methods. While planar images are useful to derive biokinetics over time, 3D dosimetry based on quantitative SPECT/CT has potential advantages over planar approaches. Although requiring more time to acquire and more complex algorithms for activity quantification, SPECT/CT fused images provide insight into organ-specific 3D activity distribution, which can then be used as input data for voxel dosimetry. Berker et al. presented a hybrid 2D/3D activity quantification technique [63]. The proposed method of integrating 2D image information into 3D image-based dosimetry can speed up SPECT/CT-based 3D dosimetry without losing accuracy.

Several factors are involved in renal toxicity during or after PRRT, among which absorbed dose to kidneys plays a key role. In fractionated external radiation therapy the absorbed dose limit for causing 5 % probability of attaining radiation nephropathy within 5 years has been found to be 23 Gy, rising to 28 Gy with 50 % probability of nephropathy [64]. This dose is typically given at a high dose rate (1–10 Gy/min) in fractions of 1.5–2 Gy. However, in PRRT, where the maximum dose rate is much lower (~3 mGy/min), decaying exponentially with the radiopharmaceutical effective half-life and the organ dose distribution is inhomogeneous, the critical dose is expected to be higher and has not yet been determined [10]. In order to transfer the external radiation therapy dose limit to a corresponding limit in radionuclide therapy, the linear-quadratic (LQ) model can be applied. BED, obtained by the LQ model, has been proved to correlate strongly with renal toxicity, in contrast to kidney absorbed doses estimated by conventional dosimetry [6]. Conclusively, BED can be used to establish an accurate dose–response relationship. Even though BED values have not yet been established, studies report a mean kidney BED value of 40 Gy for patients without risk factors [3, 6].

As has been already mentioned, the imaging radiopharmaceutical should ideally be the same with the therapeutic one. However, for ^{90}Y-labelled radiopharmaceutical imaging, quantification of the uptake and biodistribution is challenging, due to its nearly pure β-emission. In the absence of a photopeak, imaging of ^{90}Y is dependent on bremsstrahlung radiation. A number of studies investigated energy windows, collimators and scatter correction techniques for ^{90}Y bremsstrahlung imaging [13, 65, 66]. Some groups used Monte Carlo simulations in conjunction with phantom studies to optimise the accuracy of quantitative imaging, by enabling corrections to be made for attenuation, scatter and collimator-detector response [67]. These correction methods for quantification of ^{90}Y imaging

allowed the recent development of bremsstrahlung dosimetry studies, offering the opportunity for direct assessment of absorbed dose delivered in ^{90}Y PRRT [68]. In a recent study of three patients, quantitative pretherapy ^{111}In- ibritumomab SPECT/CT and planar whole-body (WB) imaging and therapy ^{90}Y-ibritumomab SPECT/CT and WB imaging, resulted in differences between absorbed-dose estimates within 25 %, except for the lungs [69]. Recently, the presence of internal positron–electron pair production in ^{90}Y was determined and the branching ratio was found to be $(31.86 \pm 0.47) \times 10^{-6}$ [70]. Thus, PET imaging of ^{90}Y might be a new method for dosimetric assessments. However, the low probability of positron emission requires large amounts of administered activity. ^{90}Y PET-based dosimetry has been so far implemented in selective internal radiation therapy of the liver, where the ^{90}Y micro-spheres are selectively located in the hepatic tumours and there is no biological removal [71].

Finally, improvements in the dosimetric process include the adoption of kidney multiregional dosimetric models. The administered dose in PRRT is limited by the radiation burden of critical organs. Studies proved inhomogeneous radioactivity distribution of the radiolabelled peptides in the kidneys [10, 72]. Ex vivo autoradiography of healthy kidney tissue, after injection of ^{111}In-DTPA-octreotide, showed that the radioactivity is localised predominantly in the proximal tubule in the cortex [73]. More accurate radiation dose estimates may be determined either by adopting multiregional models or by assuming entire uptake by the cortex. In the first case, regional dosimetric estimations are performed in different substructures of the kidney (cortex, medulla, pelvis, papillae), while in the second activity is assumed to be distributed only in the cortex, which is 70 % of the total kidney mass [73, 74].

Conclusions

The dosimetric results demonstrated large interpatient variability in tumour and organ uptake, stressing the need for personalised therapy planning. Patient-specific dosimetry in PRRT is therefore needed, in order for the fixed dose regimens to be replaced with patient-tailored therapy planning. Comparing ^{86}Y-DOTATOC to ^{111}In-DTPA-octreotide for the dosimetry of ^{90}Y-DOTATOC, the results demonstrated similar organ doses, while the tumour dose seemed to be underestimated if ^{111}In-DTPA-octreotide is used. SPECT and planar dosimetry achieved comparable results in organ dose estimation, but SPECT provided a more accurate estimate of tumour dosimetry.

Kidneys are the dose-limiting organs due to both high absorbed doses and increased radiosensitivity. Additionally, kidney absorbed doses were higher in PRRT with ^{90}Y-DOTATOC, allowing for higher ^{177}Lu activities to be administered in ^{177}Lu- DOTATATE therapies.

When comparing total tumour responses in ^{90}Y- and ^{177}Lu- PRRT schemes, ^{90}Y led to overall response (CR, PR and MR) in up to 36 % of patients, while ^{177}Lu achieved higher rates of 56 %.

Attention should be paid to the image quantification process, as it is can be a large source of error in dosimetry. In order for the dosimetry techniques to be systematically implemented in a busy clinical environment, the dosimetry software programmes can be an essential tool, as they help in making the procedures less time-intensive.

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