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ORIGINAL ARTICLE

Individualized dosimetry-based activity reduction of ^{90}Y-DOTATOC prevents severe and rapid kidney function deterioration from peptide receptor radionuclide therapy

Sofie Van Binnebeek · Kristof Baete · Bert Vanbilloen · Christelle Terwinghe · Michel Koole · Felix M. Mottaghy · Paul M. Clement · Luc Mortelmans · Karin Haustermans · Eric Van Cutsem · Alfons Verbruggen · Kris Bogaerts · Chris Verslype · Christophe M. Deroose

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Abstract
Purpose Assessment of kidney function evolution after ^{90}Y-DOTATOC peptide receptor radionuclide therapy (PRRT) with capped activity administration based on a 37-Gy threshold of biological effective dose (BED) to the kidney.

Methods In a prospective phase II study, patients with metastasized neuroendocrine tumours were evaluated for therapy using 185 MBq ^{111}In-pentetreotide with amino acid coinfusion. Planar whole-body images were acquired at four time-points after injection and kidney volumes were measured

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S. Van Binnebeek · K. Baete · B. Vanbilloen · C. Terwinghe · L. Mortelmans · C. M. Deroose
Nuclear Medicine, University Hospitals Leuven, Leuven, Belgium

S. Van Binnebeek
e-mail: sofie.vanbinnebeek@uzleuven.be

S. Van Binnebeek · K. Baete · B. Vanbilloen · C. Terwinghe · L. Mortelmans · C. M. Deroose
Department of Imaging & Pathology, KU Leuven, Leuven, Belgium

M. Koole
Department of Nuclear Medicine, University Medical Centre Groningen, Groningen, The Netherlands

F. M. Mottaghy
Department of Nuclear Medicine, University Hospital Aachen, Aachen, Germany

F. M. Mottaghy
Department of Nuclear Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

P. M. Clement
Medical Oncology, University Hospitals Leuven, Leuven, Belgium

P. M. Clement
Laboratory of Experimental Oncology, KU Leuven, Leuven, Belgium

K. Haustermans
Radiation Oncology, University Hospitals Leuven, Leuven, Belgium

K. Haustermans · E. Van Cutsem · C. Verslype
Department of Oncology, KU Leuven, Leuven, Belgium

E. Van Cutsem · C. Verslype
Division of Digestive Oncology, University Hospitals Leuven, Leuven, Belgium

A. Verbruggen
Laboratory for Radiopharmacy, KU Leuven, Leuven, Belgium

K. Bogaerts
Division of Public Health and Primary Care (I-Biostat), KU Leuven, Leuven, Belgium

C. M. Deroose (✉)
Nuclear Medicine, UZ Leuven, Herestraat 49, 3000 Leuven, Belgium
e-mail: christophe.deroose@uz.kuleuven.be

using CT/MRI. BED to the kidneys was estimated using an extended BED formula and biexponential renal clearance. Based on published BED dose–toxicity relationships, we allowed a maximal kidney BED of 37 Gy; if the calculated BED exceeded 37 Gy, treatment activity was reduced accordingly. Kidney function was assessed at baseline and at 18 months, predominantly using ^{51}Cr-EDTA. The rate of renal function decline was expressed as annual glomerular filtration rate loss (aGFRL).

Results Only 22 of 50 patients reached the 18-months timepoint, with most missing patients having died due to disease progression. In the 22 patients who reached 18 months, no rapid kidney function deterioration was observed over the 18 months, aGFRL >33 % was not seen, and only three patients showed an increase of one toxicity grade and one patient an increase of two grades. No significant correlations between kidney volume (p=0.35), baseline GFR (p=0.18), risk factors for renal function loss (p=0.74) and aGFRL were observed. Among the 28 patients who did not reach 18 months, one developed grade 4 kidney toxicity at 15 months after PRRT.

Conclusion Prospective dosimetry using a 37 Gy BED as the threshold for kidney toxicity is a good guide for ^{90}Y-DOTATOC PRRT and is associated with a low risk of rapid renal function deterioration and evolution to severe nephrotoxicity.

Keywords PRRT · Dosimetry · Renal function · ^{90}Y-DOTATOC

Introduction

Neuroendocrine tumours (NETs) are a heterogeneous group of tumours originating from neuroendocrine cells in a number of different organs. Some of these neoplasms keep the ability to produce a number of specific bioactive amines and hormones [1]. The most frequent sites of origin are the digestive tract (including the pancreas) and the lungs. Many NETs overexpress a specific G-protein-coupled transmembrane receptor on their cell surface, the somatostatin receptor (SSR), thus enabling the therapeutic use of somatostatin analogues. Peptide receptor radionuclide therapy (PRRT) with radiolabelled somatostatin analogues is a promising tool in the management of patients with inoperable or metastasized neuroendocrine tumours. Favourable clinical results have already been obtained with 1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic-acid (DOTA)-D-Phe^1-Tyr^3-octreotide (DOTATOC) labelled with ^{90}Y, a high-energy β-emitter [2–4], and with (DOTA)-D-Phe^1-Tyr^3-Thr^8-octreotide (DOTATATE) labelled with ^{177}Lu, a β/γ-emitter [5, 6].

A clear relationship has been demonstrated between reduction in tumour volume and the absorbed dose in the tumour, therefore the aim of clinical PRRT is to deliver the maximal absorbed dose to the tumour while keeping the absorbed dose to normal tissues within acceptable limits [7]. Deterioration of renal function is the activity-limiting toxicity in PRRT. The radiopeptide is reabsorbed in the proximal tubule and retained in the interstitium, leading to kidney irradiation. The coadministration of positively charged amino acids, such as L-lysine and/or L-arginine, that competitively inhibit the proximal tubular reabsorption of the radiopeptide by binding to the megalin receptor, results in reductions in the renal dose that range from 9 % to 53 % [8–11]. Despite kidney protection, renal failure may become clinically evident years after radionuclide therapy, especially following the use of ^{90}Y-DOTATOC [12], so kidney toxicity remains an issue for this therapy. In the six reported patients in whom histopathology was available, radiation-induced thrombotic microangiopathy was consistently identified in kidney biopsy samples [13–17]. Bodei et al. [10] have identified a number of risk factors for kidney toxicity after PRRT: hypertension (systolic or diastolic blood pressure >140/90 mmHg), diabetes, age (>60 years), renal morphological abnormalities (e.g. large cortical cysts), transarterial chemoembolization and previous chemotherapy with nephrotoxic agents. Other predictors, introduced by Imhof et al. [3], were low baseline glomerular filtration rate (GFR) and high renal tracer uptake in the SSR whole-body (WB) scan. Kidney size has also been linked to kidney toxicity, as described by Pauwels et al. [7] who found an increased risk in patients with smaller kidneys. In some series, kidney toxicity has resulted in rapid kidney function deterioration, with annual GFR losses (aGFRL) of 40 % to even 60 % [18].

We used a dosimetry-based patient-specific therapeutic regimen in a single-centre phase II trial with ^{90}Y-DOTATOC. The renal biological effective dose (BED) after four cycles of ^{90}Y-DOTATOC at a fixed activity (1.85 GBq/m^2 per cycle) was estimated before the start of therapy using ^{111}In-pentetreotide. Based on the method of Barone et al. [18], the maximal projected BED was fixed at 37 Gy after four cycles of ^{90}Y-DOTATOC. This BED corresponds to the inflexion point of the sigmoid kidney dose–effect curve relating kidney dose to renal function loss which, according to the model Barone et al., results in a loss in kidney function of 5.2 % annually [18]. If the kidney BED after four cycles was estimated to exceed 37 Gy, either the treatment was cancelled or the administered activity of the last treatment was reduced in order to reduce the estimated BED below 37 Gy; a minimum of three cycles at 100 % activity was required to proceed to treatment. We hypothesized that severe and rapid kidney function loss, defined as a aGFRL of more than 33 %, as was observed in originally by Barone et al. in 4 of 18 patients (22 %), would be avoided if the 37 Gy threshold was not exceeded.

Materials and methods

Study population

The study group consisted of patients with SSR-positive NETs enrolled in a phase II single-centre trial with ^{90}Y-DOTATOC in whom kidney function could be assessed 18 months after initiation of therapy. All patients were Caucasian. This trial was approved by the Ethics Commission of the University Hospitals Leuven, and all patients gave written informed consent.

First and mainly, we investigated the effects of kidney BED on kidney function in a cohort comprising 22 of the 50 patients included in the study (11 women and 11 men; age 42 – 79 years, mean: 62±11 years), 20 with a tumour of gastroenteropancreatic (GEP) origin, 1 with a primary neuroendocrine tumour in the lung and 1 with a carcinoid of unknown primary (CUP), all histologically confirmed. Clinical characteristics, previous therapies and risk factors that might have affected renal function, according to Bodei et al. [10], are summarized in Table 1. At baseline, the following procedures were performed: (1) GFR measurement by radiotracer clearance with ^{51}Cr-EDTA, (2) ^{111}In-pentetreotide scintigraphy for dosimetry (see below), and (3) ^{68}Ga-DOTATOC PET/CT for evaluation of the degree of SSR expression. For accurate determination of kidney volume, the contrast-enhanced CT data from the ^{68}Ga-DOTATOC PET/CT scan or MRI scan were used. The volume of the kidney was not delineated on the ^{68}Ga-DOTATOC PET images.

Next, in the other 28 treated patients (17 women and 11 men; age 31 – 77 years, mean 57±12 years; 20 with GEP-NETs, 2 with primary lung NETs, 2 with Merckel cell carcinomas, 2 with CUP, and 1 with primary breast and 1 primary kidney NET), a similar work-up of renal effects at 18 months after PRRT was not performed as 24 patients died before 18 months (23 because of tumour progression and 1 after prosthesis surgery for an arthritic hip), 2 patients had not yet reached the 18-month time-point (15 and 14 months at the time of this report) and in 2 patients PRRT was ended after one cycle because of aberrant biodistribution of ^{68}Ga-DOTATOC imaging at week 7 [19] and we assumed that the given (cumulative dose) was insufficient to cause nephrotoxicity. However, we still looked at the evolution of estimated GFR (eGFR) and kidney toxicity up until the last month before the patient's death. Two patients were not enrolled in the study because the calculated kidney BED was so high that even a minimum of three cycles at 100 % activity exceeded 37 Gy.

Study design

PRRT consisted of four cycles of ^{90}Y-DOTATOC using 1.85 GBq/m^2 per cycle every 8 weeks up to an estimated kidney BED of 37 Gy. Body surface area values determined using the formula of Du Bois and Du Bois [20], individual activities per cycle, total administered activity and the follow-up period are listed in Table 2.

An infusion of 2,000 ml of an amino acid solution with 6.88 g/l lysine and 10.72 g/l arginine (Proteinsteril® Hepa 8 % (Fresenius)) was given to inhibit tubular reabsorption of the radiopeptide starting 30 min before administration of the radiopharmaceutical and continued up to 4 h after administration.

Radiolabelling of ^{90}Y-DOTATOC

The procedure is discussed in the supplementary data 1.

^{111}In-pentetreotide dosimetry procedure

^{111}In-pentetreotide ($T_{1/2}$=67.3 h), prepared from a commercially available kit (OctreoScan; Mallinckrodt Medical B.V., Petten, The Netherlands), was used as a surrogate to assess the kinetic behaviour and biodistribution of ^{90}Y-DOTATOC [21]. The same amino acid solution as that used during PRRT was infused over 4 h starting 30 min before injection of 185 MBq ^{111}In-pentetreotide to create the same renal uptake conditions as during ^{90}Y-DOTATOC administration.

In each patient, multiple anterior and posterior WB images were acquired using a dual head gamma camera (ECAM; Siemens, Erlangen, Germany) with the following settings: 256×1,024 matrix, medium-energy low-penetration (MELP) collimators, and 15 % energy window centred at 171 keV (90 % abundance) and 245 keV (94 % abundance). Imaging was performed at four time-points after injection using a standard source with known activity positioned at the feet for conversion of image counts to activity concentrations in the organs. The first WB scan was acquired 15 min after administration of ^{111}In-pentetreotide at 10 cm/min and before bladder voiding. Subsequent WB scans (after voiding) were acquired at 4, 24 and 48 h at 5 cm/min. The total body counts of the first WB scan with full bladder were defined as 100 % of the administered activity. Counts on the following scans were expressed as fractions of the injected activity (FIA, expressed as percentages). Samples of ^{111}In (standard sources with known activity) were used to perform cross-calibration of the dose calibrator with (a) a gamma camera (about 1.85 MBq) and (b) a well counter (about 0.0185 MBq). Scatter correction was not performed in order to avoid underestimation of the kidney BED and attenuation correction was also not performed as we were looking at relative and not absolute values (we used the evolution of activity in one area of the body as a function of time; when assuming constant attenuation this value is not affected by attenuation). On each WB scan, regions of interest (ROI) were drawn around the standard source, total body, spleen, liver and kidneys

Table 1 Clinical characteristics

Patient	Sex	Age (years)	Primary tumour	Previous therapies	Risk factors for renal function loss
1	F	56	Small intestine	Surgery, somatostatin analogues	Cortical cyst
2	M	59	Small intestine	Interferon, somatostatin analogues	–
3	M	63	Colon	Surgery, chemotherapy, targeted agents (everolimus), somatostatin analogues, interferon	Age >60 years, diabetes mellitus, nephrotoxic chemotherapy, a functional left kidney
4	F	56	Small intestine	Surgery, somatostatin analogues	–
5	M	64	Small intestine	Somatostatin analogues	Age >60 years, diabetes mellitus, hypertension, cortical cysts
6	M	69	Small intestine	Surgery, somatostatin analogues	Age >60 years, hypertension, cortical cysts
7	F	78	Carcinoid of unknown primary	Radiation, somatostatin analogues	Age >60 years, diabetes mellitus, hypertension
8	M	69	Small intestine	Surgery, somatostatin analogues	Age >60 years
9	F	80	Small intestine	Everolimus, somatostatin analogues	Age >60 years, hypertension, cortical cysts
10	F	55	Small intestine	Surgery, interferon, somatostatin analogues, transarterial chemoembolization	Transarterial chemoembolization
11	M	50	Rectum	Surgery, somatostatin analogues	–
12	M	75	Pancreas	Sutent, somatostatin analogues	Age >60 years, hypertension
13	M	55	Small intestine	Surgery, somatostatin analogues	Hypertension
14	F	68	Small intestine	Surgery, radiofrequency ablation, somatostatin analogues	Age >60 years
15	M	58	Small intestine	Surgery, transarterial chemoembolization, somatostatin analogues	Transarterial chemoembolization
16	F	79	Small intestine	Somatostatin analogues	Age >60 years, hypertension, nephrectomy (left)
17	M	71	Pancreas	Somatostatin analogues	Age >60 years
18	F	43	Lung	Surgery, somatostatin analogues	–
19	F	65	Small intestine	Chemotherapy, somatostatin analogues	Age >60 years, hypertension
20	M	56	Small intestine	Surgery, somatostatin analogues	–
21	F	59	Small intestine	Surgery, chemotherapy, interferon, somatostatin analogues	–
22	F	42	Small intestine	Surgery, somatostatin analogues	–

(Supplementary Fig. 1). Geometric mean counts of anterior and posterior WB scans were calculated within each organ ROI, background correction was performed and the time-dependent FIA values for the total body, spleen, liver, kidneys and remainder were calculated. These FIA values were then converted to the FIA ^{90}Y-DOTATOC activities at the measured time points, with the simplified assumption that ^{111}In-pentetreotide and ^{90}Y-DOTATOC have similar biodistributions and kinetic profiles [22, 23]. For every region, nonlinear regression analysis was used to determine the radiopeptide clearance based on a biexponential model and the results were used to estimate $\tilde{a}$, the time-integrated activity coefficient, previously known as residence time (Supplementary Fig 2). The $\tilde{a}$ values were then used in the internal dosimetry software program OLINDA/EXM version 1.0 (Vanderbilt University, Nashville, TN) for a phantom model-based computation of the organ absorbed doses [24].

Tomographic views (SPECT) of the abdomen (liver and kidneys) were acquired at 8 and 24 h after injection using the same gamma camera as for the WB images with 128×128 matrix, 20 s per view and 72 views over 360°. The SPECT images were used to visually confirm suspected overestimation of kidney activity on the WB images caused by superimposition of organs with relatively high tracer uptake (metastatic foci in the liver or physiological uptake in an enlarged liver) or excretion (colon). If overestimation of kidney activity on the planar images was confirmed, this was recorded. No SPECT-based dosimetry was performed in any of the 22 study patients. In one treated patient (patient 8) a second dosimetry was performed because of an acute decrease in kidney function based on systematic intake of NSAIDS during the first dosimetry [25].

Kidney volumes were measured on pretherapeutic transverse CT images (slice thickness 3 mm; 10 of 22 patients) or MRI images (10 patients, THRIVE images, slice thickness 1.5 mm; 2 patients, T1 images, slice thickness 4 mm) by drawing ROIs on consecutive transverse slices

Table 2 Treatment characteristics

Patient	Body surface area (m^2)	Administered activities (MBq)				Total administered activity (MBq)	Total administered activity (% BED)	Follow-up (months)
		Cycle 1	Cycle 2	Cycle 3	Cycle 4			
1	1.72	2,949	3,004	3,041	3,090	12,081	400	41
2	1.82	3,482	3,541	3,304	3,574	13,901	400	18[a]
3	2.04	3,689	3,770	3,715	–	11,174[c]	300	22[a]
4	1.50	2,720	2,516	2,849	2,638	10,723	400	24[a]
5	2.25	4,096	3,837	4,166	4,148	16,247	400	27[a]
6	1.95	3,685	3,719	3,645	3,604	14,652	400	39
7	1.57	2,875	2,945	3,001	2,912	11,733	400	38
8	1.79	3,157	3,108	3,341	6,064	15,799	400	31
9	1.51	2,812	2,875	2,727	–	8,414[b]	300	34
10	1.82	3,482	3,263	3,441	–	10,186[b]	300	32
11	1.90	3,478	3,500	3,611	3,422	14,012	400	32
12	1.87	2,686	3,448	3,419	3,519	13,072	400	30
13	2.10	3,844	3,704	3,929	3,855	15,333	400	29
14	1.62	3,049	2,993	2,965	–	8,998[b]	300	28
15	2.08	3,848	3,578	3,867	3,904	15,196	400	27
16	1.53	2,612	2,842	2,979	–	8,432[c]	300	26
17	1.93	2,842	3,737	3,693	2,953	13,224[b]	380	24
18	1.76	3,252	3,282	3,138	3,067	12,739	400	22
19	1.58	2,882	2,505	2,975	–	8,362[b]	300	19[a]
20	1.79	3,279	3,282	3,286	3,289	13,135	400	21
21	1.71	3,167	3,186	3,234	3,149	12,735	400	20
22	1.84	3,434	3,271	3,400	3,415	13,520	400	18
Mean	1.80	3,157	3,268	3,351	3,538	12,280		
Median	1.81	3,266	3,277	3,323	3,419	12,739		27
Minimum	1.50	2,612	2,505	2,727	2,638	8,362		
Maximum	2.25	4,096	3,837	4,166	6,064	16,247		
Standard deviation	0.20	424	391	380	783	2,274		
Interquartile range (Q1 – Q3)	1.64 – 1.92	2,877 – 3,482	2,996 – 3,569	3,011 – 3,637	3,084 – 3,667	10,836 – 13,806		

Numbers that do not add up are due to rounding effects

[a] Patient died from tumour progression at that time during follow-up

[b] Reduced treatment activity because $BED_{400\%}$ >37 Gy (dosimetry analysis)

[c] Reduced treatment activity because of only one functioning kidney

including the whole kidney parenchyma. All kidney delineations were performed by the same observer. The kidney mass of the phantom model in OLINDA/EXM was adjusted using the kidney volume derived from CT or MRI data.

^{90}Y-Bremsstrahlung SPECT images were obtained at one time-point after PRRT (18 h) on a single SPECT camera, as a SPECT/CT camera had not been installed in our department at the start of study. These images were only used as a qualitative assessment; absolute quantification based on ^{90}Y-bremsstrahlung was beyond the scope of this study.

Pretherapeutic kidney dose estimation

Kidney dosimetry was assessed using the Medical Internal Radiation Dose (MIRD) methodology, which assumes a uniform activity distribution within the kidneys [26]. Since peptides are mainly deposited in the proximal tubules in the renal cortex which is associated with a greater radiobiological sensitivity, the localization of the absorbed dose may increase the risk of renal toxicity. In MIRD pamphlet no. 19, the kidney is further divided into the cortex, medulla and renal pelvis compartments which allows calculation of the average dose to the cortex [27].

The absorbed dose to the kidney was prospectively estimated using the projected total administrated activity (= projected absorbed dose at 400 % of one cycle), and retrospectively calculated, using the total administrated activity (= absorbed dose for administered activity; Table 3) and the results of OLINDA using the patients' kidney volume derived from CT or MRI data. Barone et al. used the MIRD 19 models to demonstrate that the BED is a more appropriate quantity than absorbed dose to predict the dose–response relationship for renal toxicity in PRRT [18]. The BED relates absorbed dose and dose rate to radiosensitivity and repair using the linear quadratic model. More precisely, the BED gives the absorbed dose that should be delivered to a tissue for a certain biological effect at an infinitesimally small dose rate and is useful for comparing treatments with different dose rates and fractionation schemes. The use of the BED concept for renal dosimetry was expanded upon in MIRD pamphlet no. 20 [28]. The time of appearance and dose-dependence of radiation damage in normal tissue depend on its proliferative behaviour. For the kidney, the same α/β ratio (2.6 Gy) and the same half-time of DNA repair (2.8 h), as in the study Barone et al., were used and these values are generally accepted in the literature. These fixed numbers originate from data in a mouse model, although analyses of data from human tissues on DNA repair kinetics are in fact limited. However, the agreement between human and animal data is generally considered acceptable [29].

Table 3 Kidney parameters

Parameter	Value
Kidney mass (g)	
In 11 women (21 kidneys[a])	
Interquartile range (Q1 – Q3)	214 – 475
Mean	302
In 11 men (21 kidneys[a])	
Interquartile range (Q1 – Q3)	307 – 617
Mean	403
Treatment activity given (% of full dose)	400 % (in 15 patients)
	300 % (in 6 patients)
	380 % (in 1 patient)
Cumulative absorbed $D_{\text{given activity}}$ to the kidneys (Gy)	
Range	16 – 43
Mean	23
SD	6
Median	21
Interquartile range (Q1 – Q3)	20 – 25
Cumulative $\text{BED}_{\text{given activity}}$ to the kidneys (Gy), biexponential fit	
Range	18 – 31
Mean	27
SD	7
Median	24
Interquartile range (Q1 – Q3)	23 – 31
Cumulative $\text{BED}_{\text{given activity}}$ to the kidneys (Gy), monoexponential fit	
Range	19 – 55
Mean	29
SD	9
Median	27
Interquartile range (Q1 – Q3)	24 – 32

$D_{given\ activity}$ Cumulative absorbed dose to the kidneys from the activity which was given to the patient, $BED_{given\ activity}$ cumulative biological effective dose to the kidneys from the activity which was given to the patient

[a] One patient with one functioning kidney

The $\text{BED}_{400\%}$ was defined as the cumulative projected BED that a patient's kidneys would receive if the patient received the total activity scheduled in the study (i.e. BED with four cycles at 100 % of one cycle, i.e. 400 % of one cycle) and the $\text{BED}_{\text{actual}}$ (i.e. cumulative BED for the total actual administered activity) to the kidneys for every patient was estimated with an extension of the BED using biexponential clearance of the source organ based on the method of Baechler et al. [26], in which the extended BED relates the absorbed dose and time-dependent dose-rate with radiosensitivity and repair of radiation damage using the standard linear quadratic (LQ) model. The following equation was applied:

$$\text{BED} = D_i \times \left(1 + (\text{G} \times D_i) \Big/ (\alpha/\beta)\right)$$

where D_i is the kidney dose delivered per cycle i, α/β is the quotient of the intrinsic radiosensitivity (α) and the potential sparing (β) capacity of the kidney tissue which was set as α/β=2.6 Gy [30], G is the Lea-Catcheside factor for a biexponentially decaying source (see Eq. 14 in Baechler et al. [26]) which is calculated using the effective clearance rate constants λ_1 and λ_2, the dose-rate fraction coefficients of the biexponential model and the exponential repair rate constant μ (which quantifies the rate of sublethal damage repair with μ=2.8 h) [26, 30].

To allow comparison with previously published BED results by Barone et al. [18], we recalculated our $\text{BED}_{400\%}$ and our $\text{BED}_{\text{actual}}$ with the same equation as in that publication:

$$\text{BED} = \sum\nolimits_i D_i + \beta/\alpha \times T_{1/2\ \text{rep}} \Big/ \left(T_{1/2\ \text{rep}} + T_{1/2\ \text{eff}}\right) \times \sum\nolimits_i D_i^2$$

Where D_i is the dose delivered for cycle i, $T_{1/2\ \text{eff}}$ is the effective half-life of ^{90}Y-DOTATOC based on ^{111}In-octreotide renal clearance, $T_{1/2\ \text{rep}}$ is the repair half-time of sublethal damage with $T_{1/2\ \text{rep}}$=2.8 h and α/β=2.6 Gy as mentioned above [10, 18, 21]. All BED results are presented in Table 4.

Table 4 Kidney doses

Patient	$BED_{400\%}$ (Gy)		BED_{actual} (Gy)	
	Using linear quadratic model with monoexponential fit	Using extended BED formula[a] with biexponential fit	Using linear quadratic model with monoexponential fit	Using extended BED formula[a] with biexponential fit
1	29	27	27	25
2	26	24	26	25
3	36	34	27	25
4	26	24	25	23
5	26	24	25	23
6	21	20	21	21
7	24	22	24	22
8	29	28	28	27
9	73	52	55	39[b]
10	67	64	51	48[b]
11	19	18	19	18
12	32	30	30	28
13	25	24	25	23
14	44	45	33	34
15	24	23	24	23
16	26	25	19	18
17	43	40	40	37
18	24	23	24	22
19	52	48	37	34
20	22	21	22	21
21	36	34	36	34
22	28	26	27	26
Mean	33	31	29	27
Median	27	25	27	24
Minimum	19	18	19	18
Maximum	73	64	55	48
STDEV	15	12	9	7
Interquartile range (Q1 – Q3)	25 – 36	24 – 34	24 – 32	23 – 31

[a] See Baechler et al. [26]

[b] Probable overestimation of kidney doses due to planar dosimetry effects (superimposition of bowel/liver metastasis on kidneys)

Assessment of renal function

Renal function was evaluated using the series of tests shown in Table 5.

Estimated glomerular filtration rate

Kidney function was assessed at baseline, and at 6, 12 and 18 months after PRRT. The serum creatinine concentration was determined using the Jaffé method until October 2012 (in 20 patients) and an enzymatic method from November 2012 to the present (2 patients). However, both methods are traceable by isotope dilution mass spectrometry and differences were proven to be negligible.

The eGFR was calculated using the MDRD (modification of diet in renal disease) formula (supplementary data 2) [31]. The difference between serum creatinine and eGFR at 18 months and baseline (ΔS-creat and ΔeGFR) was calculated.

Measured glomerular filtration rate

The measured GFR (mGFR) was determined by measuring the clearance of the radiotracer ^{51}Cr-EDTA. An activity of 3.7 MBq ^{51}Cr-EDTA was injected intravenously and blood samples were taken at 1, 2, 3 and 4 h after injection and the ^{51}Cr-EDTA blood concentrations measured. mGFR was further calculated by applying an appropriate mathematical

Table 5 Evolution of renal function

Patient	Baseline serum creatinine (mg/dl)	Percentage change in serum creatinine at 18 months	Baseline GFR[a] (ml/min/1.73 m^2)	Baseline kidney toxicity (grade)	Percentage change in GFR[a] at 18 months	Annual GFR loss (%)[b]		Kidney toxicity at 18 months (grade)	Risk factors	Time to grade 4 toxicity[c] (years)	
						Linear	Exponential			Linear extrapolation	Exponential extrapolation
1	0.74	8	71	0	2.6	2.0	2.0	0	Yes	>25	>25
2	0.85	21	94	0	20.7[d]	14.0[d]	11[d]	0	No	6[d]	16[d]
3	1.76	9	54	2	10.3[d]	6.7[d]	6[d]	2	Yes	12[d]	15[d]
4	0.57	4	76	0	5.1[d]	3.3[d]	11[d]	0	No	13[d]	18[d]
5	0.71	−7	91	0	22.2	14.7	15.3	0	Yes	5	11
6	0.84	55	73	0	21.9	14.7	15.3	2	Yes	3.9	10
7	0.84	19	75	0	17.4	11.3	11.7	0	Yes	5	13
8	1.05	6	60	1	12.3	8.0	8.2	2	Yes	5	17
9	0.63	14	74	0	12.3	8.0	8.2	2	Yes	>25	>25
10	0.51	27	100	0	3.0	2.0	2.0	0	Yes	5	9
11	0.77	5	104	0	−11.4	−7.3	−7.2	0	No	–[e]	–[e]
12	0.65	18	95	0	33.2	22.0	23.4	0	Yes	3.6	7
13	0.84	19	87	0	−4.7	−3.3	−3.3	0	Yes	–[e]	–[e]
14	0.94	Not available	65	0	5.4	3.3	3.4	0	Yes	14	>25
15	1.08	30	64	1	20.0[d]	13.3[d]	10.4[d]	2	Yes	7[d]	15[d]
16	0.97	−7	50	2	−9.1[d]	−6[d]	−9.4[d]	1	Yes	–[d,e]	–[d,e]
17	0.75	0	85	0	−20.4	−13.3	−12.9	0	Yes	–[e]	–[e]
18	0.73	18	112	0	17.2[d]	11.3[d]	2.1[d]	0	No	7[d]	>25[d]
19	0.56	25	100	0	22.9[d]	15.3[d]	15.6[d]	0	Yes	7[d]	11[d]
20	1.00	9	84	0	23.4	15.3	16.0	0	No	4.5	10
21	1.05	33	67	0	10.9	7.3	7.5	1	No	7	21
22	0.72	8	88	0	9.5	6.0	6.1	0	No	12	>25

[a] GFR was calculated using ^{51}Cr-EDTA unless indicated otherwise

[b] Annual GFR loss determined using linear and exponential fitting of GFR values

[c] Kidney toxicity grade was determined according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, based on cGFR at 18 months unless indicated otherwise

[d] GFR was estimated using the MDRD formula using serum creatinine at 18 months

[e] No GFR loss during first year

model. The clearance of ^{51}Cr-EDTA was calculated in all patients at baseline and in 15 patients at 18 months after the first treatment with ^{90}Y-DOTATOC. The difference between the mGFR at 18 months and the mGFR at baseline was calculated (ΔmGFR). In the other seven patients, kidney function was not assessed by ^{51}Cr-EDTA clearance because of declining health (four patients) and incomplete follow-up (three patients), but the eGFR based on the MDRD formula was used. The difference between eGFR at 18 months and at baseline was also calculated (ΔeGFR).

It must be highlighted that aGFRL was never calculated using different methods at baseline and target, so in these seven patients the eGFR was used and in 15 patients the mGFR was used at baseline and 18 months after the first cycle of PRRT.

Annual glomerular filtration rate loss

The rate of renal function decline per year was expressed as aGFRL (based on mGFR in 15 patients and on eGFR in 7 patients in whom mGFR was not available), and was calculated using both exponential and linear regression. The correlations between aGFRL and relevant clinical parameters (kidney size, BED, risk factors for renal function loss, kidney volume and baseline GFR) were determined.

Kidney toxicity grade

The grade of kidney toxicity was assessed on the basis of GFR at baseline and at 18 months using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (see Supplementary data 3). The correlations between kidney toxicity grade and BED and renal function risk factors were determined. The hypothetical time for kidney function to reach grade 4 toxicity was also calculated assuming that the rate of kidney function loss (aGFRL) would remain constant by both linear and exponential extrapolation.

Patients without renal function assessment at 18 months

In the 28 of 50 treated patients without renal function assessment at 18 months the evolution of eGFR (from the MDRD formula) and kidney toxicity until the last month before the patient's death were evaluated. aGFRL was also calculated in patients surviving at least 9 months after PRRT (13 of 28, 46 %).

Statistical analysis

See Supplementary data 4.

Results

Clinical and treatment characteristics are presented in Tables 1 and 2, respectively, and kidney parameters in Table 3.

Renal function, kidney toxicity and risk factors

In all 50 patients, renal function was normal before treatment with mGFR ranging from 50 to 128 ml/min/1.73 m^2 (mean 79±19 ml/min/1.73 m^2). Of the 50 treated patients, 22 were available for kidney function assessment at 18 months (Table 4; for the other patients, see section Patients without renal function assessment at 18 months). The evolution of their GFR over 18 months is shown in Fig. 1. No rapid deterioration of kidney function (no creatinine increase of >50 %) was observed during the 18-month follow-up. The GFR, using mGFR in 15 patients and eGFR in 7 patients, ranged from 35 to 116 ml/min/1.73 m^2 (mean 72±19 ml/min/1.73 m^2, with a mean loss of 9.5±20.3 % and a maximal loss of 36 % at 18 months. The mean difference between baseline GFR and GFR at 18 months was 11±14 % (range −20 % to 33 %).

In all 22 patients with kidney follow-up at 18 months, the mean exponential aGFRL after ^{90}Y-DOTATOC PRRT was 7±9 % (range 0 to 23 %; Table 5). aGFRL was less than 10 % in 12 patients, less than 20 % in 9 patients and more than 20 % in 1 patient (patient 12). This patient had preexisting risk factors for renal function loss (age >60 years and hypertension; Table 1). In the total group of patients, there was no significant difference in exponential aGFRL between patients with and without risk factors (Fig. 2a; p=0.92; Wilcoxon rank-sum test). In contrast to Imhof et al. [3], we found no significant correlation between baseline GFR and aGFR loss (r = 0.29, p = 0.18, Spearman correlation; Fig. 2b).

At 18 months, grade 1 nephrotoxicity was observed in two patients and grade 2 nephrotoxicity in four patients; no relationship was found between the presence of preexisting risk

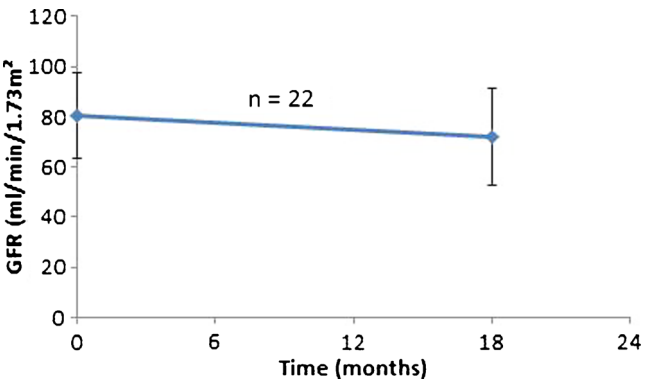

Fig. 1 Evolution of mean GFR over 18 months (absolute values) after the first ^{90}Y-DOTATOC PRRT cycle. No rapid deterioration in kidney function is apparent (*error bars* SD)

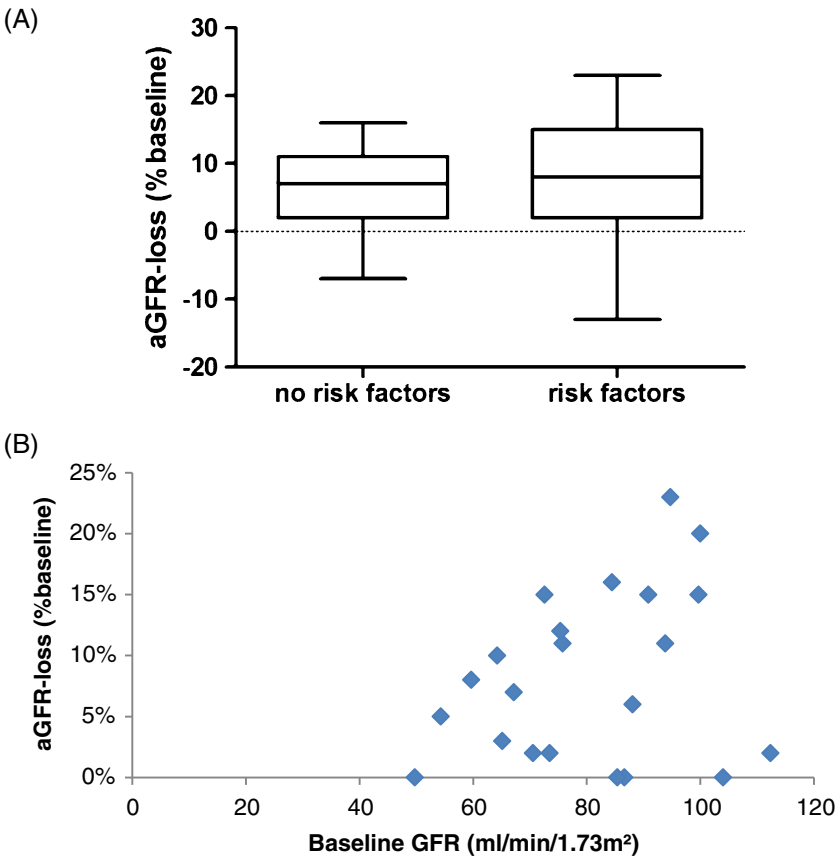

Fig. 2 **a** Relationship between the presence of risk factors and exponential aGFRL (p=0.92, Wilcoxon rank-sum test). **b** Relationship between baseline GFR and aGFRL (r=0.29, p=0.18, Spearman correlation)

factors for renal function loss and kidney toxicity at 18 months (p>0.99, Fisher's exact test; Fig. 3a). In the patient with aGFRL >20 %, the kidney toxicity score remained 0. We also examined the changes in kidney toxicity score between baseline and 18 months: in 17 patients (77 %) the toxicity grade was unchanged, in 3 patients (14 %) toxicity increased by one grade, in 1 patient (4.5 %) toxicity improved by one grade, and in 1 patient (4.5 %) toxicity increased from grade 0 to grade 2 (Fig. 3b). In this last patient, however, right-sided ureterolithiasis was discovered on a follow-up CT scan 12 months after PRRT that led to progressive hydronephrosis and loss of kidney parenchyma, together with an increase in creatinine clearance loss. Shock wave lithotripsy (SWL) was performed at 25 months after PRRT that was followed by stabilization, but without recovery of creatinine clearance. Dimercaptosuccinic acid scintigraphy was also performed after lithotripsy and showed diminished right kidney uptake with absence of uptake in the upper pole. The contribution of the right kidney to the total renal function was only 20 %. As the mGFR at 18 months was 54 ml/min/1.73 m^2, the extra loss in GFR due to ureterolithiasis can be estimated at 38 ml/min/1.73 m^2 and the toxicity grade without would be 0.

The times to grade 4 toxicity estimated by linear extrapolation (which yields less optimistic results than exponential extrapolation) were ≥25 years in six patients (27 %), ≥10 years in four patients (18 %), ≥5 years in nine patients (41 %) and <5 years in three patients (14 %; Table 5).

Kidney volume

The mean kidney volume was 302±70 ml in women and 403 ±94 ml in men with wide ranges (214 – 475 ml in women and 307 – 617 ml in men). In all the men and in 6 of the 11 women, the kidney volume was larger than the that of the standard Oak Ridge National Library (ORNL) phantom [24]. No correlation was found between kidney volume and renal function loss, and in particular the presence of smaller kidneys was not associated with a greater risk of renal function loss (Fig. 4a; r=0.15, p=0.48, Spearman correlation). There was also no significant correlation between kidney volume and BED (Fig. 4b; r=−0.14, p=0.54, Spearman correlation).

Kidney BED assessment

Cumulative absorbed doses based on the actual total activity that each patient received during PRRT ranged between 16 and 43 Gy (mean 23 Gy, median 21 Gy, interquartile range, IQR, 20 – 25 Gy). The $BED_{400\%}$ using the LQ model with monoexponential fitting ranged between 19 and 73 Gy (mean 33±15 Gy, median 27 Gy, IQR 25 – 36 Gy) and between 18

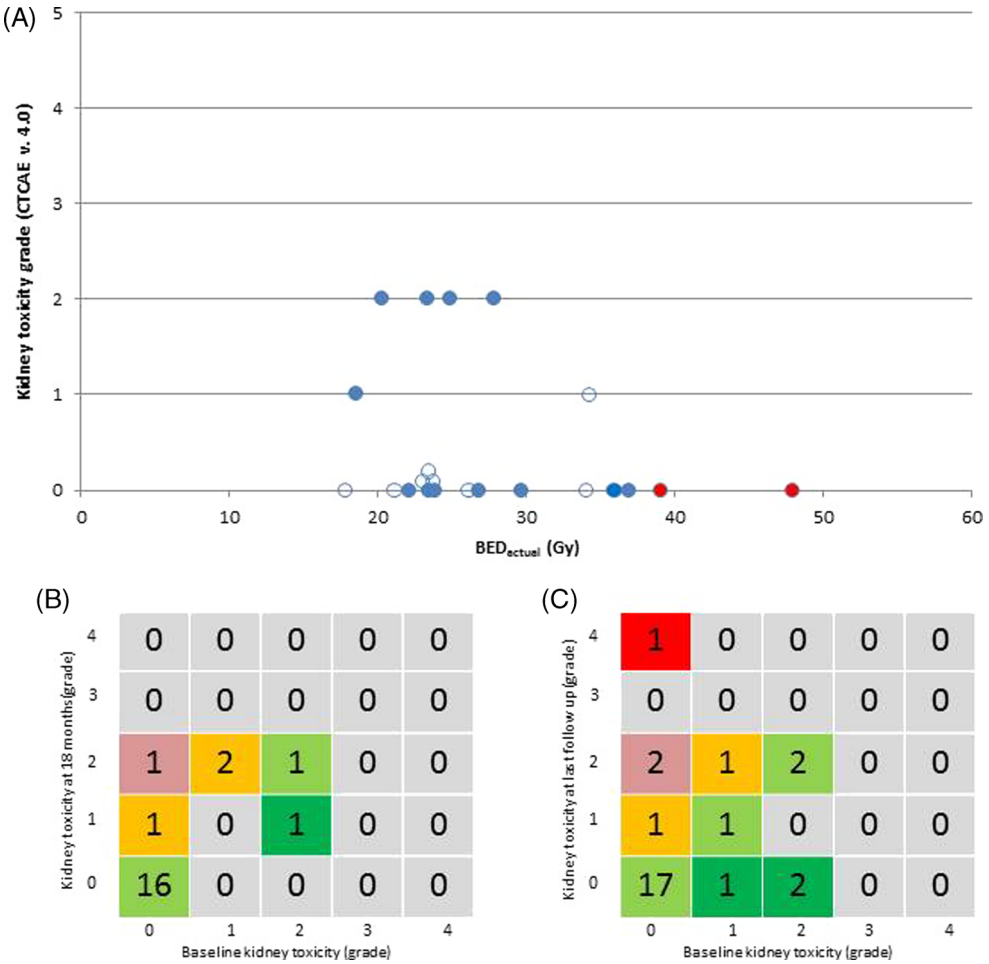

Fig. 3 **a** Relationship between BED_{actual} and kidney toxicity in 22 patients. The *filled circles* represent patients with risk factors for renal function loss (15 patients), and the *open circles* patients without risk factors (7 patients). The *red circles* represent the two patients with >37 Gy kidney BED_{actual} with overestimation of the dosimetric result; both also had risk factors (three points are slightly misplaced to avoid overlap). **b**, **c** Evolution of kidney toxicity grade in relation to baseline (**b**) at 18 months in 22 patients with intense assessment of renal function evolution, and (**c**) at the time of the last follow-up in 28 patients who did not survive until the 18-month time-point

and 64 Gy (mean 31±12 Gy, median 25 Gy, IQR 24 – 34 Gy) using the extended formula with biexponential fitting (Table 3). The BED_{actual} calculated with the LQ model and monoexponential fitting ranged between 19 and 55 Gy (mean 29±9 Gy, median 27 Gy, IQR 24 – 32 Gy). The BED_{actual} calculated using the extended formula with biexponential fitting ranged between 18 and 48 Gy (mean 27±7 Gy, median 24 Gy, IQR 23 – 31 Gy; Tables 3 and 4). Overall, the $BED_{400\%}$ and the BED_{actual} values were slightly lower when the extended BED formula was used, with a mean difference in $BED_{400\%}$ of 6.5 % (95% CI 4.2 – 8.8; p=0.01, paired t test) and in BED_{actual} of 6.4 % (95% CI 4.1 – 8.8; p=0.005, paired t test) with the difference in $BED_{400\%}$ ranging from −2.5 % to 29.1 % and the difference in BED_{actual} from −2.7 % to 29.0 %.

Correlation between kidney BED and renal function loss

The calculated $BED_{400\%}$ was below 37 Gy except in 5 of the 22 patients. Therefore, in these 5 patients, the total administered activity was reduced to 300 % of one cycle in four patients and 380 % in one patient, resulting in a BED_{actual} of <37 Gy with the exception of patient 9 ($BED_{400\%}$ 52 Gy, BED_{actual} 39 Gy) and patient 10 ($BED_{400\%}$ 64 Gy, BED_{actual} 48 Gy). In these patients the results of dosimetry were not accurate because of superimposition of bowel and liver metastasis over the kidney ROI on the planar WB images and consequently a BED_{actual} higher than 37 Gy (39 Gy and 48 Gy, respectively) was accepted (Supplementary Fig. 3). This value has to be interpreted as an upper boundary of BED, not as an accurate computation. Only 300 % of the activity of one cycle was also administered in the two patients with only one functioning kidney (patients 3 and 16, $BED_{400\%}$ 34 Gy and 25 Gy, respectively).

There was no significant correlation between kidney BED_{actual} calculated with the extended BED formula and loss in kidney function expressed as aGFRL (Fig. 5; r=0.07, p= 0.76, Spearman correlation). In patients 9 and 10 in whom BED_{actual} exceeded 37 Gy aGFRL was 2 % and 20 %, respectively, which is within the range observed in the other patients, confirming the hypothesis that these BED_{actual} values are overestimated. In the two patients with dose reduction due to only one functioning kidney, the aGFRL was 6 % in patient 3 and no aGFRL was observed in patient 16.

We also compared the observed aGFRL in all 22 patients with the data from the 18 patients investigated by Barone et al. [18]. We used BED_{actual} calculated with the LQ model with monoexponential fitting (the same method as used by Barone

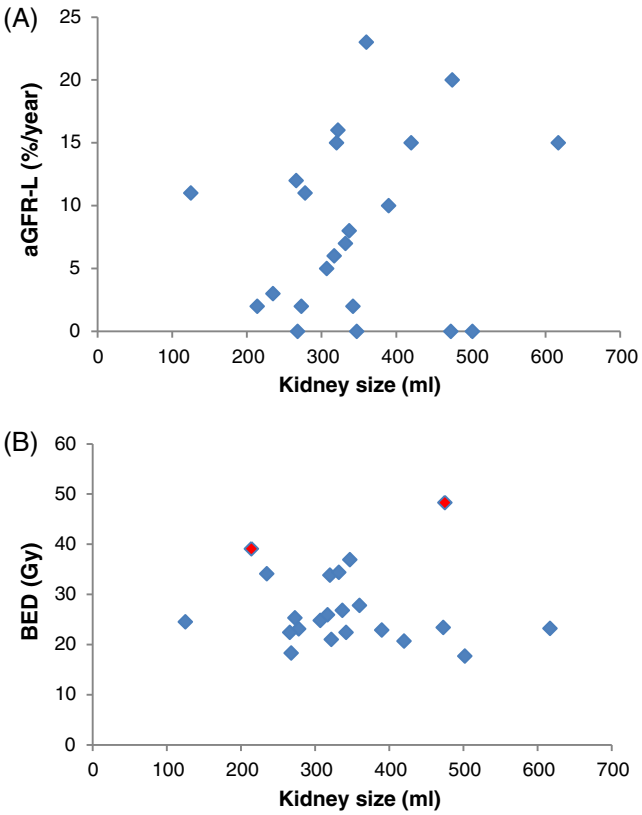

Fig. 4 Relationships between kidney size and (**a**) aGFRL (r=0.15, p=0.48, Spearman correlation), and (**b**) BED_{actual} (r=−0.14, p=0.54, Spearman correlation) in 22 patients. The *red diamonds* represent the two patients with kidney BED_{actual} >37 Gy with overestimation of the dosimetric result. Correlations were not significant

et al.) and the corresponding observed aGFRL in our patients and added these data to the published graph of Barone et al. (Fig. 6). None of the patients in our series showed an increase in aGFRL of >33 %, not even the two treated patients with a BED_{actual} >37 Gy. Furthermore, most of our data points were located to the left of the fit. In the BED_{actual} range between 20 and 30 Gy, the dose–effect curve of Barone et al. underestimates the aGFRL by an average of 8.8 % (95% CI 5.0 – 12.7, p=0.002, paired t test).

Finally, we examined the benefit of activity reduction in the five patients with $BED_{400\%}$ >37 Gy and the two patients with only one functioning kidney. We calculated the aGFRL, in terms of full treatment activity (400 %) and using the fit of the BED–aGFRL graph of Barone et al. [18], and compared it to the observed aGFRL (Table 6). There was a benefit in four out of the seven patients (mean 9.4±17.3 %, range −10.5 – 39.9 %). The best results were obtained in patients 9 and 10 in whom the BED was overestimated due to superimposition.

Patients without renal function assessment at 18 months

In these 28 out of the 50 treated patients, the mean kidney follow-up time assessing eGFR was 7 months (range 0.5 – 18 months). Based on their BED result, the treatment activity was reduced in 16 of these 28 patients, and in two patients PRRT was ended after one cycle because of aberrant biodistribution of ^{68}Ga-DOTATOC imaging at week 7 (BED_{actual} 3.3 Gy and 8.4 Gy) [19]. Only 15 of the 28 patients received the prescribed activity; the other 13 died during PRRT because of disease progression. There was no marked decrease in eGFR observed in 27 out of those 28 patients. In the 13 patients who reached the 9-month time-point after the first PRRT, aGFRL ranged from 0 % to 32 %, except in one patient with aGFRL of 66 %. The toxicity grade stayed the same in 19 patients or decreased one or two grades in 3 patients during PRRT. The toxicity grade increased in four patients, by one grade in two and by two grades in two, during therapy (Fig. 3c). The patient with aGFRL of 66 % developed renal failure and grade 4 nephrotoxicity (starting with grade 0 toxicity at baseline) at 15 months with serum creatinine 8.4 mg/dl and eGFR <15 ml/min/1.73 m^2 (Supplementary

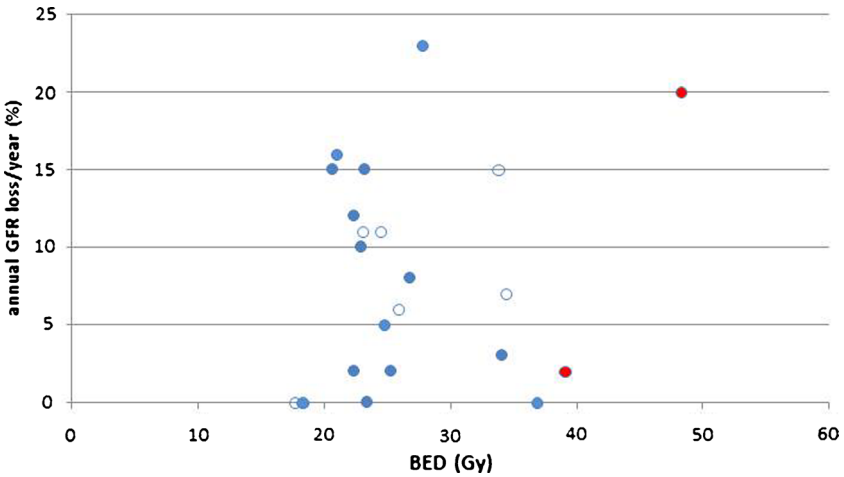

Fig. 5 Relationship between BED_{actual} and aGFRL in 22 patients. The *filled circles* represent patients with risk factors. The correlation between BED_{actual} and aGFRL was not significant (p=0.76, r=0.07, Spearman correlation)

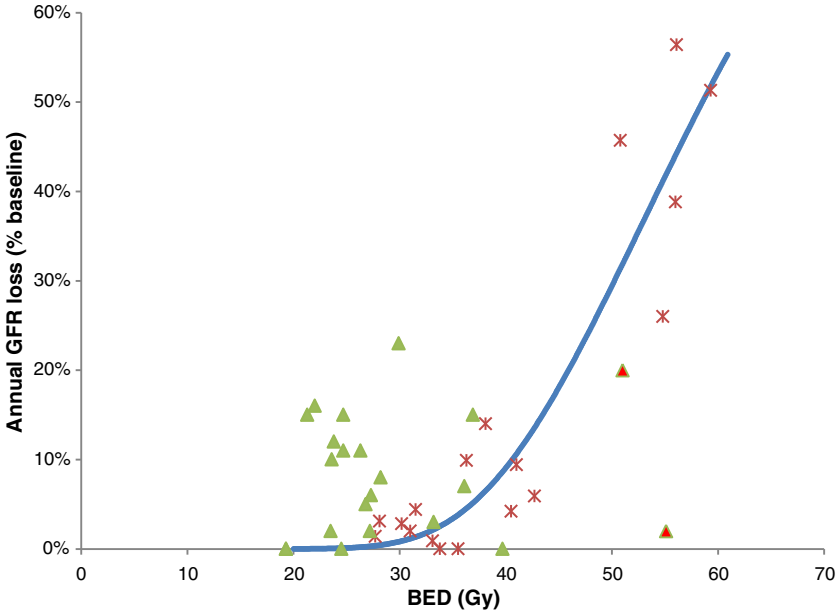

Fig. 6 Relationship between BED_{actual} (using the LQ model with monoexponential fitting) and aGFRL. The *red crosses* are the data of Barone et al. [18], the *green triangles* are our data from 22 patients. None of our patients showed an increase in aGFRL of >33 %, not even the two treated patients with a BED_{actual} >37 Gy (*red triangles*). This prospectively validates the use of the 37 Gy BED threshold proposed by Barone et al. [18]. Furthermore, most of our data points are located to the left of the fit

data 5). A kidney biopsy showed moderate acute tubule necrosis; there were no positive arguments for thrombotic microangiopathy.

Two patients were excluded from the study because the calculated kidney BED was so high that even a minimum of three cycles at 100 % activity exceeded 37 Gy ($BED_{400\%}$ 57 Gy and 64 Gy).

Discussion

The kidney is the major critical organ during PRRT. After filtration by the glomeruli, radiolabelled peptides are reabsorbed and retained in the proximal tubular cells [32]. Due to the activity present in the (relatively radioresistant) tubular cells, renal toxicity arises through irradiation of the radiosensitive glomeruli and medulla [12, 14, 33]. With external beam radiotherapy (EBRT), the critical dose to the kidney is 23 Gy. At this dose, a 5 % probability of attaining radiation nephropathy within 5 years has been reported [10, 18, 30, 34]. The LQ model can be used to convert the EBRT dose limit to a corresponding limit in radionuclide therapy [30]. Barone et al. [18] have calculated the tissue complication probability curve for ^{90}Y-DOTATOC-PRRT, relating the kidney BED to aGFRL. They showed that the probability increases at 37 Gy BED.

The objective of this study was to use prospective individualized dosimetry data to administer ^{90}Y-DOTATOC up to a maximum kidney BED threshold of 37 Gy. There are some differences between our study and that of Barone et al.: (1) different patient population, (2) different dosimetry tracer (^{111}In-octreotide versus ^{86}Y-DOTATOC); (3) different dosimetry methodology (planar vs. tomographic). In the BED_{actual} range between 20 and 30 Gy, the Normal Tissue Complication Probability (NTCP) curve of Barone et al. underestimates the aGFRL by an average of 6.7 % which can be explained by the different dosimetry protocols used. Nevertheless, none of our patients showed pronounced and rapid kidney function deterioration, and the aGFR loss was acceptable in every patient. This observation prospectively validates the use of the 37 Gy BED as a critical dose threshold predicting rapid kidney deterioration.

From among the 50 patients included in the study, we thoroughly studied the 22 who survived until the 18-month follow-up time-point, but we also looked at the data from the 28 other patients who died or were lost to follow-up before 18 months after PRRT. Two of those 22 patients received a total administered activity that resulted in a calculated BED_{actual} of >37 Gy (patients 9 and 10). This value is an upper limit and not an accurate estimate because of superimposition effects during planar dosimetry.

We found no correlation between kidney size and aGFRL. This was expected because the individual kidney volumes were already taken into consideration during dosimetry by delineating the kidneys on CT or MRI images and replacing the phantom kidney values in OLINDA by the individual volumes in every patient. When calculating the BED to the kidneys using fixed administered activity protocols and using standard kidney volumes instead of individual kidney size, the renal dose would be underestimated if the kidneys are smaller than those of the standard model. This is explained by the concentration of the same activity in a smaller volume, which increases the radiation dose to the kidneys. Pauwels et al. [7] prospectively calculated the absorbed doses to the kidneys using standard ORNL volumes, and found that smaller kidneys have a greater risk of function loss. If the kidney size is

Table 6 aGRFL based on the LQ model (similar to the calculations of Barone et al. [18])

Patient	$BED_{400\%}$ (Gy)	$aGFRL_{400\%}$ (%)[a]	BED_{actual} (Gy)	$aGFRL_{actual}$ (Gy)[b]	$aGFRL_{observed}$ (%)[c]	ΔaGFRL (actual − observed)
1	29	0.6	27	0.3	2.0	−1.7
2	26	0.1	26	0.2	11.2	−11.1
3[d]	36	4.4	27	0.2	5.4	−5.2
4	26	0.2	25	0.1	11.3	−11.2
5	26	0.1	25	0.1	15.3	−15.2
6	21	0.0	21	0.0	15.3	−15.2
7	24	0.0	24	0.1	11.7	−11.6
8	29	0.7	28	0.4	8.2	−7.7
9[d]	73	77.0	55	41.9	2.0	39.9
10[d]	67	67.8	51	31.9	19.7	12.2
11	19	0.0	19	0.0	−7.2	7.2
12	32	1.5	30	0.8	23.4	−22.6
13	25	0.1	25	0.1	−3.3	3.4
14[d]	44	16.4	33	2.2	3.4	−1.2
15	24	0.1	24	0.0	10.4	−10.4
16[d]	26	0.2	19	0.0	−9.4	9.4
17[d]	43	14.1	40	8.6	−12.9	21.5
18	24	0.1	24	0.0	2.1	−2.0
19[d]	52	35.0	37	5.1	15.6	−10.5
20	22	0.0	22	0.0	7.5	−7.5
21	36	4.2	36	4.3	16.0	−11.6
22	28	0.3	27	0.3	6.1	−5.8

aGFRL annual rate of GFR loss determined using exponential fitting of GFR values calculated using ^{51}Cr-EDTA except in patients 2, 3. 4, 15, 16, 18 and 19 in whom it was estimated using serum creatinine at 12 months or at 18 months, both using the MDRD formula

[a] Projected aGFRL at 400 % treatment activity

[b] aGFRL calculated for given activity

[c] Observed aGFRL

[d] Patients in whom the dose was reduced because of a projected BED of >37 Gy or because of only one functioning kidney

[e] Beneficial effect of dose reduction on aGFRL

known, the decision whether or not to perform PRRT should be taken after dosimetry based on the actual kidney size.

Taking the risk factors for kidney function loss described by Bodei et al. [10] and Imhof et al. [3] into account, no significant difference in aGFRL was found between patients with and without risk factors. It needs to be emphasized that no dosimetry was performed in the patients from the series of Imhof et al. This supports the hypothesis that it is not the presence of risk factors, but the actual dose delivered to the kidneys that is more important for predicting kidney toxicity. Patients with risk factors should not be treated differently based only on the presence of these risk factors, but should be treated according to their individual kidney BED.

Valkema et al. found a median decline in creatinine clearance of 7.3 % per year in patients treated with ^{90}Y-DOTATOC and 3.8 % per year in patients treated with ^{177}Lu-DOTATATE [12]. This difference was explained by the type of β-particle, and more specifically the range of the β-particle, used for therapy. The range of β-particles from ^{90}Y is maximally 12 mm, and the range of the ^{177}Lu electrons is maximally 2.1 mm. As the average distance from the tubular uptake and the glomerulus is important for the estimation of the radiation damage after PRRT, the sensitive glomeruli may be partially spared using ^{177}Lu, the range of ^{90}Y on the other hand is long enough to reach the glomeruli. This means that 1 Gy from ^{177}Lu may lead to a lower average glomerular dose than 1 Gy from ^{90}Y, and this may be an additional explanation for the much lower average decline in creatinine clearance in the patients treated with ^{177}Lu-DOTATATE than in those treated with ^{90}Y-DOTATOC. In a very recent study, Romer et al. [35] found that the rate of severe permanent renal toxicities was similar for ^{90}Y-DOTATOC and ^{177}Lu-DOTATOC (9.2 % and 7.8 % respectively; p=0.32). According to this study, ^{177}Lu-labelled peptides could cause just as much renal toxicity as ^{90}Y-labelled peptides. However, a possible bias in this study cannot be excluded as the study was not randomized. Ideally, a randomized controlled clinical trial should be performed.

Among the 1,109 patients treated with ^{90}Y-DOTATOC by Imhof et al. [3], 9 % developed severe permanent renal toxicity after PRRT and in an earlier study by Bodei et al. [10], WHO grade 1 – 3 creatinine toxicity was seen in 9 of 23 patients selected for dosimetric studies from a group of 211 patients. In the study by Imhof et al. it is not clear if all patients received the same amino acid combination. and in the study by Bodei et al. four of the nine patients with renal function impairment did not receive any amino acids. In a multicentre trial [4], transient grade 3 or 4 renal toxicity was seen in 3 of 90 patients (3 %). In studies by Kwekkeboom et al. [36, 37], no renal toxicity was seen after treatment with ^{177}Lu-octreotate, but the follow-up period was no longer than

6 months which is insufficient to predict long-term renal toxicity after treatment with ^{177}Lu-DOTATATE.

There were a number of limitations to this study. Our study population was small (22 of 50 treated patients, as only 22 patients survived until the 18-month time-point), but this is in line with other dosimetry studies that also looked at patient populations of similar size (e.g. 28 patients [10], 18 patients [18]). Our study population comprised all successive patients eligible for treatment within the study. We had insufficient follow-up to assess long-term kidney function outcome.

We used a dosimetry protocol with sequential ^{111}In-pentetreotide WB scans for calculation of quantitative dosimetry. SPECT acquisitions were only used for visual assessment in the event of superimposition, not for quantitative assessment. However, multiple WB scans can offer sufficient information on biodistribution and its variation over time [21]. The introduction of SPECT/CT would allow refinement of dosimetry procedures and multiple SPECT/CT acquisitions of, for example, the critical organs and/or principal tumour burden are advocated. This study was initiated before the installation of a SPECT/CT system in our department, so its use was not an option. We observed some patients in whom pure planar dosimetry resulted in overestimation of organ doses due to superimposition of metastasis or bowel activity over kidney tissue; a SPECT(/CT)-based dosimetry approach would have overcome this limitation. Nevertheless, rapid deterioration in kidney function was observed in only one patient. Although the pathology report did not show the hallmarks of nephrotoxicity after PRRT, a possible influence of PRRT has to be assumed. The subsequent aGFR loss was acceptable in every patient up to 18 months, with exception of the aforementioned patient (1 of 50, 2 %).

Dosimetry with ^{86}Y-DOTATOC seems theoretically more suitable as ^{86}Y is the almost perfect chemical surrogate for ^{90}Y and makes high-resolution PET possible, but ^{86}Y-DOTATOC has a short half-life (14.7 h), has low availability and interferes with high-energy gamma rays, which reduce the feasibility and accuracy of the data collection for dosimetry. ^{111}111In-Octreotide on the other hand is approved by EMA, is reimbursed and commercially available. ^{86}Y-DOTATOC was not available in our country for legal and logistic reasons. Helisch et al. [23] and Förster et al. [22] compared the biodistribution of ^{86}Y-DOTATOC with that of ^{111}In-pentetreotide and concluded that adequate dosimetry prior to ^{90}Y-DOTATOC therapy is mandatory and that kidney dosimetry with both compounds is possible and similar. ^{111}In-Pentetreotide also has a very important advantage for dosimetry compared to ^{86}Y-DOTATOC, as the physical half-life of ^{111}In is 67.3 h, and is thus comparable with that of ^{90}Y (64 h) and with the biological half-life of peptides, which allows derivation of time–activity curves.

Other radiotracers that can be used for dosimetry in ^{90}Y-DOTATOC PRRT are ^{111}In-DOTATOC, ^{90}Y-bremsstrahlung planar images or SPECT and ^{90}Y-PET images. Some authors have suggested the use of ^{111}In-DOTATOC because it mimics the therapeutic agent better than ^{111}In-DTPA-octreotide, and this agent has been used in some clinical protocols for dosimetric purposes. Conventional bremsstrahlung imaging is already widely used for assessing biodistribution after ^{90}Y-ibritumomab tiuxetan therapy, and after ^{90}Y-SIR therapy. The use of ^{90}Y-bremsstrahlung images for dosimetry after ^{90}Y-DOTATOC PRRT is still under investigation. Fabbri et al. have shown that ^{90}Y-bremsstrahlung images acquired and reconstructed by hybrid SPECT/CT systems using adequate calibration factors can provide better information on distribution and biokinetics of ^{90}Y-DOTATOC, and that patient-specific dosimetry is feasible with acceptable accuracy following each therapy cycle [38]. ^{90}Y-PET acquisition has been shown to be feasible for dosimetry assessment after liver SIRT in an anatomical phantom as well as in a patient [39, 40]. In a phantom study, Walrand et al. found that ^{90}Y-DOTATOC PET can be used for kidney dosimetry, but this is currently not being done on patient data [41]. This has to be further explored.

Finally, to allow comparison with previously published BED results [18], we recalculated our $BED_{400\%}$ and our BED_{actual} using the same equation as used in the previous study. However, in contrast to Barone et al., who used a linear (4 – 24 h) and a monoexponential (24 – 48 h) fit, we used a monoexponential fit to our four data points, assuming that this did not lead to any relevant changes in outcome.

Despite the different chemical structures, the different radionuclides and peptides and the different dosimetry protocols, the proposed approach has been shown to be sufficiently reliable to correctly predict a high radiation burden to critical organs. At the time of initiation of the study in 2008, planar dosimetry was still standard and a SPECT/CT system was not yet available in our department. Dosimetry refinement was not the main objective of our study and we opted for a protocol feasible in patients receiving antiemetogenic medication. We used the dosimetry results as a tool to improve the safety of PRRT administration. We opted for serial planar dosimetry using a predefined threshold of 37 Gy BED from the model of Barone et al. This objective was achieved, as rapid deterioration in kidney function and evolution to severe nephrotoxicity was avoided in 98 % of the patients (49 of 50), which is a result similar to or better than found in other ^{90}Y-DOTATOC PRRT studies with [7, 12] or without [3, 4] tomographic dosimetry.

Over the last 5 years, much effort has been directed towards improving the accuracy of image analysis and quantification for dosimetry (e.g. 3-D quantitative SPECT imaging as detailed in MIRD 23, individualized Monte Carlo simulations, voxel-level analysis, correction methods for positron emitters

with coemission of high-energy photons). We therefore advocate the use of quantitative SPECT/CT in future dosimetry studies in accordance with MIRD 23, as it would allow refinement of dosimetry compared to planar imaging based dosimetry, especially when superimposition of tumour or physiological activity over the kidney tissue is suspected.

Conclusion

Our observations confirm that a prospective dosimetry protocol in which an amino-acid solution is simultaneously coadministered and in which a BED of 37 Gy is used as a threshold for kidney toxicity based on published data [18] is a good guide for ^{90}Y-DOTATOC PRRT. The use of this protocol avoided rapid deterioration in renal function and evolution to severe nephrotoxicity in 98 % of patients (49 of 50). Although this dosimetry protocol has its shortcomings, it is feasible in nuclear medicine departments for those seeking to become familiar with PRRT if basic equipment and trained personnel are available. Moreover, this dosimetry protocol results in an acceptable clinical outcome, especially in patients with a high kidney BED.

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Conflict of interest The authors declare that they have no conflict of interest.

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