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ORIGINAL ARTICLE

Personalized ^{177}Lu-octreotate peptide receptor radionuclide therapy of neuroendocrine tumours: initial results from the P-PRRT trial

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Abstract

Purpose Peptide receptor radionuclide therapy (PRRT) is mostly administered using a fixed injected activity (IA) per cycle. This empiric regime results in highly variable absorbed doses to the critical organs and undertreatment of the majority of patients. We conceived a personalized PRRT protocol in which the IA is adjusted to deliver a prescribed absorbed dose to the kidney, with the aim to safely increase tumour irradiation. We herein report on the initial results of our prospective study of personalized PRRT, the P-PRRT Trial (NCT02754297).

Methods PRRT-naïve patients with progressive and/or symptomatic neuroendocrine tumour (NET) were scheduled to receive a four-cycle induction course of ^{177}Lu-octreotate with quantitative SPECT/CT-based dosimetry. The IA was personalized according to the glomerular filtration rate and the body surface area for the first cycle, and according to the prior renal Gy/GBq for the subsequent cycles. The prescribed renal absorbed dose of 23 Gy was reduced by 25–50% in case of significant renal or haematological impairment. Responders were allowed to receive consolidation or maintenance cycles, for each of which 6 Gy to the kidney were prescribed. We simulated the empiric PRRT regime by fixing the IA at 7.4 GBq per cycle, with the same percentage reductions as above. Radiological, molecular imaging, biochemical, and quality of life responses, as well as safety, were assessed.

Results Fifty-two patients underwent 171 cycles. In 34 patients who completed the induction course, a median cumulative IA of 36.1 (range, 6.3–78.6) GBq was administered, and the median cumulative kidney and maximum tumour absorbed doses were 22.1 (range, 8.3–24.3) Gy and 185.7 (range: 15.2–443.1) Gy respectively. Compared with the simulated fixed-IA induction regime, there was a median 1.26-fold increase (range, 0.47–2.12 fold) in the cumulative maximum tumour absorbed dose, which was higher in 85.3% of patients. In 39 assessable patients, the best objective response was partial response in nine (23.1%), minor response in 14 (35.9%), stable disease in 13 (33.3%) and progressive disease in three patients (7.7%). In particular, 11 of 13 patients (84.6%) with pancreatic NET had partial or minor response. The global health status/quality of life score significantly increased in 50% of patients. Acute and subacute side-effects were all of grade 1 or 2, and the most common were nausea (in 32.7% of patients) and fatigue (in 30.8% of patients) respectively. Subacute grade 3 or 4 toxicities occurred in less than 10% of patients, with the exception of lymphocytopenia in 51.9% of patients, without any clinical consequences however. No patient experienced severe renal toxicity.

Conclusions Personalized PRRT makes it possible to safely increase tumour irradiation in the majority of patients. Our first results indicate a favourable tolerance profile, which appears similar to that of the empiric regime. The response rates are promising, in particular in patients with NET of pancreatic origin.

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Keywords Personalized · Peptide receptor radionuclide therapy · ^{177}Lu-octreotate · Dosimetry · Neuroendocrine tumours

Introduction

Peptide receptor radionuclide therapy (PRRT) with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-octreotate) is an effective palliative treatment for neuroendocrine tumours (NETs). In patients with progressive midgut NET, PRRT has been shown superior to high-dose long-acting octreotide in terms of objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) [1]. Other series have also shown the efficacy of PRRT in other NETs such as pancreatic NET (pNET) [2, 3]. Furthermore, ^{177}Lu-octreotate PRRT has consistently yielded very low severe toxicity rates [1, 3, 4]. However, ^{177}Lu-octreotate PRRT has been mostly administered following an empiric regime of four cycles of a fixed injected activity (IA) of 7.4 GBq, despite the fact that the absorbed doses per IA to critical organs (kidney and bone marrow, BM) are highly variable between patients [1, 3–7]. The moderate ORRs and low toxicity observed so far suggest that many, if not most patients are being undertreated with this empiric regime.

A personalized approach to PRRT could make it possible to optimize tumour absorbed dose in individual patients by standardizing absorbed doses to critical organs up to safety thresholds. This can be done by personalizing the number of 2-monthly, fixed-IA cycles, as proposed by two Swedish groups [5, 6]. However, this approach results in a high variability in the number of cycles, and hence in the intensity of the induction course [5]. To overcome this issue, we instead proposed personalizing the IA per cycle to reach the prescribed absorbed dose of 23 Gy to the kidney. Our simulation study suggested that, using this approach, tumour absorbed doses could be increased by 1.5 fold, on average, during a 4-cycle induction course [7]. Based on this simulation, we launched a prospective study of personalized PRRT, the P-PRRT trial. Here, we report our preliminary results of dosimetry, safety, and efficacy.

Materials and methods

Study design

The P-PRRT trial is an ongoing, prospective, open-label, single-centre, phase 2 study of personalized ^{177}Lu-octreotate PRRT at CHU de Québec – Université Laval. This study is registered at ClinicalTrials.gov (NCT02754297) and started in April 2016.

Patients

Although the study is open to patients with prior exposure to PRRT, this analysis concerns only PRRT-naïve patients treated before February 2018. The cohort analysed here is independent from our retrospective cohort of patients treated with empiric PRRT before April 2016 [7]. Eligibility criteria include progressive and/or symptomatic NET of any origin, and tumour uptake greater than that of the liver (i.e., Krenning score of 3 or 4) on ^{111}In-octreotide scintigraphy or ^{68}Ga-octreotide/octreotate positron emission tomography (PET). There are no strict exclusion criteria other than pregnancy or breast feeding. Relative contraindications such as poor performance status and marked haematological or renal impairment are judged based on clinical assessment of potential risks vs benefits, as this study also has the compassionate objective to facilitate access to PRRT. The Institutional Ethics Committee approved this study, and all patients provided informed consent to participate.

Personalized PRRT

^{177}Lu chloride was purchased from IDB Holland BV (Baarle-Nassau, The Netherlands), and DOTA-octreotate was generously provided by the Erasmus Medical Center (Rotterdam, The Netherlands). ^{177}Lu-octreotate radiolabelling was performed as previously described, utilizing 16 μg of peptide per μg of irradiated ^{176}Lu mass to ensure a minimum 2:1 peptide:Lu molar ratio [3]. Intravenous anti-nausea premedication (16 mg ondansetron and 8 mg dexamethasone) and nephroprotective amino acids (25 g L-lysine dihydrochloride and 25 g L-arginine dihydrochloride dissolved in 1 l of normal saline, infused over 4 hours) were routinely administered [3]. Somatostatin analogue treatment was continued during PRRT in patients with hormonal symptoms. The intended induction course consisted of four cycles administered at 8- to 10-week intervals. Patients responding to the induction course were eligible for consolidation, salvage, and/or maintenance cycles for further therapeutic management. Hepatic intra-arterial infusion was permitted and offered to patients with hepatic-only or largely predominant NET disease, starting at the second induction cycle. If the tumour-to-kidney ratio of absorbed doses increased by at least 10% for at least one lesion, as compared to the i.v. infusion, and despite any interfering therapeutic response, intra-arterial infusion could be continued for the subsequent cycles.

We prescribed a renal absorbed dose of 5 Gy for the first cycle, a cumulative dose of 23 Gy during the induction course, and 6 Gy for each additional cycle (i.e., consolidation,

salvage, and maintenance cycles) [7]. This prescription was reduced by 25% (17.25 Gy) or 50% (11.5 Gy) in case of baseline haematological or renal impairment of grade 2 or 3 respectively, using the definitions from the Common Toxicity Criteria for Adverse Events (CTCAE, version 4.03). The personalized IA at the first induction cycle was calculated from the estimated glomerular filtration rate (eGFR) and body surface area (BSA), as previously described [7]. For the second and subsequent cycles, the prescribed IA was calculated according to the renal absorbed dose per IA received at the first cycle or the mean renal absorbed dose per IA from the two prior cycles, in order to deliver the remaining prescribed renal absorbed dose divided equally among the remaining induction cycles. Any increase in IA was limited to 50% above the highest IA ever received by the patient, unless there was significant subacute haematological toxicity. In such cases, the increase was limited to 25% in case of grade 2 toxicity, or no increase in case of grade 3 toxicity [7].

Dosimetry

After each administration of ^{177}Lu-octreotate, quantitative single-photon emission computed tomography/computed tomography (QSPECT/CT) covering at least the liver, the kidneys, and the dominant tumours was performed approximately at 4, 24, and 72 h using a Symbia T6 camera (9.5 mm crystal, medium-energy low-penetration collimator; Siemens Healthcare, Erlangen, Germany), calibrated using previously described methods relying on multiple SPECT/CT acquisitions of low- to high-activity sources with and without surrounding attenuation medium [7, 8]. In brief, the acquisition was performed using a 128 × 128 matrix (4.8 mm voxel), 96 projections (48 per head) and 15 to 20 s per projection. The 208 keV (20% window width) photopeak data was reconstructed with ordered subset expectation maximization (four iterations, eight subsets), with scatter correction (triple-energy window, 10% scatter windows width), attenuation correction (CT-based μ-map), and resolution recovery (Flash 3D, Siemens Healthcare). Additional contiguous energy windows were acquired to monitor the average count rate over a wide spectrum of energy (17 to 550 keV) to determine dead time and correct for it [8]. Using a batch file processing script, the reconstructed SPECT file was converted into multiple PET-like slices (DICOM *PT* modality), where voxel data was expressed as Bq/ml and could be displayed as standardized uptake value (SUV) normalized for body weight.

QSPECT-based dosimetry has been performed using Hermes Gold (Hermes Medical Solutions, Stockholm, Sweden) or MIM Encore (MIM Software Inc., Cleveland, OH, USA) software, using the small volume of interest (VOI) technique [7, 9]. The serial QSPECT/CTs were co-registered using CT rigid registration. At each time point, the renal, BM, and tumour dosimetry was analysed as we previously published [7]. In brief, the activity concentration, expressed as mean SUV, was sampled using 2-cm spherical VOIs manually placed on the right and left renal parenchyma (over an area of representative parenchymal uptake), centrally in the L4 and L5 vertebral bodies (or elsewhere in the axial skeleton when required to avoid obvious metastases) for the BM self-dose, over up to five dominant tumour lesions (over the area of maximum uptake), and in the proximal thighs as a measure of background activity concentration. Renal, BM, and background uptake values from the two VOIs were averaged. The activity retention in the parts of the body not included in the QSPECT/CT volume was estimated by extrapolating the low-grade background activity concentration, and added to the activity retention measured within the QSPECT field of view. This total body retention estimation was then used to calculate the BM cross-dose. The SUVs were plotted against time, assuming a constant SUV from time of administration until the Day 0 scan, followed by a linear variation until the Day 1 scan, and then a monoexponential decay fitted through the Day 3 data to infinity. In cases where the SUV increased between Day 1 and Day 3, a linear fit was applied between the latter time points, and SUV was assumed to be constant from Day 3 onwards. The activity concentration expressed as SUV was then converted back to Bq/ml, integrated to infinity, and multiplied by an activity concentration dose factor for self-absorbed dose of 87 mGy·ml/MBq·h for kidneys and BM_{self}, and 84 mGy·ml/MBq·h for the tumour (calculated for 300-g and 4-g sphere models respectively, using OLINDA/EXM software data, version 1.0, Vanderbilt University, Nashville, TN, USA), while for computation of BM_{cross}, time-integrated total body activity was multiplied by photon-only dose factors of 1.09×10^{-4} mGy/MBq·h for males or 1.29×10^{-4} mGy/MBq·h for females (photon dose factors from total body to BM, for adult male and female models respectively; OLINDA/EXM). It is noteworthy that the BM and tumour dosimetry was observational, as it did not influence the IA prescription.

Empiric PRRT simulation

In our prospective cohort, we simulated an empiric PRRT regime where the IA per cycle was set to 7.4 GBq (or 5.5 or 3.7 GBq in cases of haematological or renal impairment of grade 2 or 3 respectively). The per-cycle renal, BM, and tumour absorbed doses were obtained by multiplying the simulated fixed IA by the actual absorbed doses per IA. Cumulative IA and doses were computed for the induction course.

Efficacy

Contrast-enhanced CT and molecular imaging (^{111}In-octreotide or ^{68}Ga-octreotide/octreotate scan, same as

baseline) were prescribed 3 months after completion of the induction course. The radiological response was evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1) and the Southwest Oncology Group (SWOG) solid tumour response criteria, including a minor response (MR) category [3, 4, 7, 10].

The molecular imaging response was visually assessed at each non-initial ^{177}Lu-octreotate cycle by comparing the maximum intensity projection (MIP) images of the Day 3 QSPECT with that of the first cycle. MIP images were also used to compare ^{68}Ga-octreotide/octreotate PET scans, while for ^{111}In-octreotide scan, the 24-h whole-body planar images were used. Because the tumour burden is represented in two dimensions on both planar and MIP images, we used a set of criteria analogous to the SWOG criteria. The size variation of the total SSTR-positive NET burden was assessed visually, as follows: progressive disease (PD) = 25% or more increase in overall tumour area; stable disease (SD) = less than 25% tumour shrinkage or progression; minor response (MR) = 25 to 50% tumour shrinkage; partial response (PR) = 50% or more tumour shrinkage; complete response (CR) = disappearance of all NET lesions. PD* category was attributed when SSTR-positive NET disease was not progressive on molecular imaging, but there was evidence of new or progressive, SSTR-negative lesion(s) on anatomical imaging. Two reviewers independently categorized each non-initial ^{177}Lu-QSPECT and follow-up ^{111}In-octreotide or ^{68}Ga-octreotide/octreotate scans and, in case of disagreement, a consensus was made with a third reviewer. It should be noted that clinical progression/deterioration or NET-related death were considered PD at any time, while SD category required at least 3 months of stability (i.e., stability until at least the 3rd cycle was required before attribution of SD as the best response).

The symptomatic and quality of life (QOL) responses were evaluated using the European Organization for Research and Treatment of Cancer (EORTC) QOL questionnaires QLQ-C30 (core module) and QLQ-GINET21 (NET-specific module) at baseline and at 3 months after the induction course [11]. The QoL scores were transformed to 0–100 scales, and differences of at least 10 points in global health status (GHS)/QOL and symptom scores were considered significant [11–13].

Biochemical response was assessed at least 3 months after completion of the induction course, using the following criteria: PD = increase of 50% or more of serum chromogranin A (Cg-A); SD = decrease or increase of less than 50% of Cg-A; PR = decrease of at least 50% in Cg-A; CR = previously elevated Cg-A falling within normal range.

Overall survival (OS) and progression-free survival (PFS) were calculated starting from the date of the first P-PRRT cycle.

Safety

Acute and subacute (up to 72 h and 2 months after each ^{177}Lu-octreotate administration, respectively) side-effects were recorded. Blood counts and liver and kidney biochemistry were performed prior to and 2, 4, and 6 weeks after each cycle, as well as 3 months after the induction course and as per routine clinical follow-up thereafter. Using CTCAE (version 4.03), subacute toxicities were assessed for each cycle, while chronic toxicity was assessed only in patients for whom data was available 3 months after the induction course.

Dose-effect relationships

In individual lesions (up to five per patient), the variation of the largest linear dimension (as in RECIST) or the products of two linear dimensions (as in SWOG) were correlated to the lesion absorbed dose cumulated during the induction course. The subacute and chronic variations in blood counts were correlated with the per-cycle and cumulative BM absorbed doses respectively. The chronic variation of eGFR was correlated with the cumulative renal absorbed dose. Per-cycle and cumulative renal, BM, and maximum tumour ($Tumour_{max}$) absorbed doses per IA (Gy/GBq) were correlated between each other.

Statistical analysis

Data are presented as the mean ± SD or median and range according to the normality of data distribution. Pearson or Spearman correlation were performed, as appropriate, for the assessment of dose–effect relationships. The Kaplan–Meier method was used to assess PFS and OS, and the inverse Kaplan–Meier method was used to estimate the follow-up time. Two-tailed paired *t*-test or Wilcoxon test were used for two-group data comparisons. A P value of 0.05 or less was considered statistically significant. Data were analysed using GraphPad Prism software (version 7, GraphPad Software Inc., La Jolla, CA, USA).

Results

Patients and treatment administration

Fifty-two patients with metastatic NET were treated with P-PRRT. Patient characteristics are presented in Table 1. One hundred and seventy-one cycles (170 induction cycles and one maintenance cycle) were administered during the study period. Inter-arterial administrations were performed in three patients (5.8%) with predominant liver disease: one received three intra-arterial cycles (second, third, and fourth cycles), while the two others received one intra-arterial cycle each (the second cycle).

In nine patients (17.3%), the induction course was interrupted: one (1.9%) withdrew after one cycle and was lost to follow-up; three (5.8%) had PD after two cycles, of whom

Table 1 Patient characteristics ($n = 52$)

Characteristic	
Gender: no. (%)	
– Female	28 (53.8)
– Male	24 (46.2)
Age: median [range]	
– At diagnosis	55.6 [17.7–78.6]
– At first cycle	61.3 [26.1–84.5]
Baseline weight loss: no. (%)	9 (17.3)
Site of the primary tumour: no. (%)	
– Pancreas	20 (38.5)
– Midgut	18 (34.6)
– Adrenal gland [a]	4 (7.7)
– Lung	3 (5.8)
– Colon	1 (1.9)
– Stomach	1 (1.9)
– Esthesioneuroblastoma	1 (1.9)
– Unknown	4 (7.7)
Grade: no. (%)	
– G1	7 (13.5)
– G2	25 (48.1)
– G3	3 (3.8)
- Unknown	18 (34.6)
Metastases to: no. (%)	
– Liver	45 (86.5)
– Lymph nodes	43 (82.7)
– Bone	24 (46.2)
– Lung	6 (11.5)
– Other [b]	24 (46.2)
Tumour burden: no. (%)	
– Extensive	1 (1.9)
– Moderate	44 (84.6)
– Limited	7 (13.5)
Tumour uptake (Krenning score): no. (%)	
– 4	39 (75.0)
– 3	12 (23.1)
– 2	1 (1.9)
Hormonal symptoms: no. (%)	33 (63.5)
Previous treatments: no. (%)	
– Somatostatin analogues	40 (76.9)
– Surgery	29 (55.8)
– Everolimus and/or sunitinib	19 (36.5)
– Chemotherapy	15 (28.8)
– Loco-regional therapy	13 (25.0)
– Empiric PRRT	0 (0.0)
– ^{131}I-MIBG	2 (3.8)
Concomitant treatments: no. (%)	
– Somatostatin analogues	32 (61.5)
– Sunitinib	1 (1.9)
Baseline laboratory abnormalities: no. (%)	
– Haemoglobin < 100 g/l	7 (13.5)
– Lymphocyte < 1.5×10^9/l	7 (13.5)
– eGFR < 60 ml/min/1.73 m^2	6 (11.5)
– Neutrophil < 1.5×10^9/l	2 (3.8)
– White blood cell < 3.0×10^9/l	1 (1.9)

eGFR, Estimated glomerular filtration rate; MIBG, meta-iodobenzylguanidine

[a] Two patient with pheochromocytoma and two patients with paraganglioma

[b] Peritoneum, ovary, subcutaneous, meninges, pleura

two died at 2.6 and 8.1 months respectively; two (3.8%) had their fourth cycle withheld because of a major therapeutic response seen on post-PRRT scan of the third cycle; one (1.9%) died from an unrelated gastrointestinal bleeding (angiodysplasia) at 4.9 months, after the second cycle; one (1.9%) suffered a grade 4 subacute neutropenia after the third cycle; and one (1.9%) developed major depression and decided to withdraw after the third cycle. Thirty patients (57.7%) received four induction cycles, among whom three died at 9.9, 10.2, and 15.9 months respectively. The induction course was still ongoing for 13 patients (25.0%).

Dosimetry

Per-cycle dosimetry for 170 cycles (dosimetry data was incomplete for one of 171 cycles), as well as cumulative dosimetry in 34 patients who received three to four induction cycles, are compared with dosimetry figures of the simulated empiric regime in Table 2, Fig. 1, and Fig. 2. Supplementary Tables 1 to 3 present the dosimetric details of these 34 patients. The median per-cycle personalized IA was 8.8 GBq (range, 0.7–32.4 GBq), representing a median 1.24-fold, and up to a 4.38-fold increase in IA over the fixed-IA regime (Fig. 1a). The peptide mass per IA was 36.0 ± 5.5 μg/GBq, resulting in a median 299 (range, 22–1130) μg of administered peptide mass per cycle. The median cumulative personalized IA over the induction course was 36.1 GBq (max,78.6 GBq), significantly higher than the median fixed IA of 23.1 GBq ($P < 0.0001$; Fig. 1b). Importantly, the cumulative median renal absorbed dose was less variable between patients under the personalized protocol (range, 8.3–24.3 Gy) than it was when simulating the empiric regime (range, 5.9–47.0 Gy; Fig. 1d). The median cumulative tumour$_{max}$ absorbed dose was significantly higher, at 185.7 Gy (max, 443.1 Gy) vs 136.7 Gy (max, 358.6 Gy; $P < 0.0001$; Fig. 1f), for the personalized and the empiric regimes respectively. Accordingly, personalized PRRT allowed a median 1.26-fold (max, 2.12 fold) increase in the cumulative tumour$_{max}$ absorbed dose, compared with the simulated empiric regime. Among the 34 patients

Table 2 Dosimetry of personalized PRRT and comparison with simulated empiric PRRT

	Per cycle ($n = 170$)			Cumulative, per induction course ($n = 34$ [a])		
	Personalized	Empiric	Ratio	Personalized	Empiric	Ratio
Injected activity (GBq)	8.8 (0.7–32.4)	7.4 (3.7–7.4)	1.24 (0.12–4.38)	36.1 (6.3–78.6)	23.1 (14.8–29.6)	1.25 (0.43–2.66)
Absorbed doses (Gy)						
Kidney	5.2 (1.8–10.5)	3.9 (1.7–23.6)	1.24 (0.12–4.38)	22.1 (8.3–24.4)	14.8 (5.9–47.0)	1.34 (0.34–2.59)
Bone marrow	0.29 (0.04–1.47)	0.23 (0.03–1.20)	1.24 (0.12–4.38)	1.17 (0.52–4.25)	0.91 (0.35–3.40)	1.31 (0.40–2.65)
Tumour (maximum)	43.7 (2.3–277.6)	31.1 (1.0–236.7)	1.24 (0.12–4.38)	185.7 (15.2–443.1)	136.7 (12.9–358.6)	1.26 (0.47–2.12)
Absorbed doses per injected activity (Gy/GBq)						
Kidney	0.54 (0.24–4.25)			0.56 (0.28–2.52)		
Bone marrow	0.035 (0.004–0.216)			0.031 (0.012–0.139)		
Tumour (maximum)	4.4 (0.1–32.0)			4.8 (0.5–16.1)		

Data is presented as median (range)

[a] Thirty patients received four induction cycles and four patients received three induction cycles

who completed at least three induction cycles, 29 (85.3%) received a cumulative personalized IA that was higher than the empiric IA (Fig. 2a) and, consequently, a higher cumulative $tumour_{max}$ absorbed dose (Fig. 2b). No patient received a cumulative renal absorbed dose substantially higher than the reference 23-Gy threshold during the induction course (max, 24.3 Gy; Fig. 3). It is of note that we found a very high inter-patient variability of the renal absorbed dose per IA, ranging from 0.24 to 4.25 Gy/GBq (Table 2).

Efficacy

In 39 patients assessable for objective response and survival, following a median follow-up of 9.5 months (range: 2.6–16.9 months; $n = 39$), the best response was PR/MR in 23 patients (59.0%), SD in 13 patients (33.3%), and PD in three patients (7.7%) (Table 3). No patient had CR. Interestingly, the subgroup of 13 patients with pNET had better response rates: PR/MR in 11 (84.6%) and SD in two (15.4%), with no patient progressing as the best response (Table 4). The per-PRRT molecular imaging response predicted the RECIST and SWOG radiological responses, except in two patients who both had progression of non-avid lesions seen on follow-up scans. Molecular imaging allowed to assess the therapeutic response in one patient with predominant bone disease who was not evaluable according to the RECIST or the SWOG criteria. The median PFS was 15.9 months, and OS was not reached (Fig. 4).

Fourteen patients completed the QOL questionnaires 3 months after the induction course (Supplementary Table 4). There was a significant improvement of the GHS/QOL score ($P = 0.005$), and the latter improved in 50% of patients. Improvement of symptoms such as pain, fatigue, and diarrhoea was observed in 42.9%, 42.9%, and 35.7% of patients respectively.

Of 16 patients with serum Cg-A assessment 3 months after the induction course, seven patients were not evaluable for biochemical response due to interfering treatment with proton pomp inhibitors ($n = 6$) or Cg-A values within the normal range before and after the induction course ($n = 1$). Of the nine assessable patients, the biochemical response was: PR in two patients (22.2%) and SD in six patients (66.7%), and PD in one patient (11.1%).

Safety

Acute and subacute side-effects of personalized PRRT are presented in Table 5. Twenty-five (48.1%) and 19 (36.5%) of patients experienced acute and subacute side-effects respectively (within 72 h and 2 months of PRRT administration respectively), all of which were of grade 1 or 2. The most common acute side-effect was nausea (32.7%), which was probably due to the amino acid infusion in most cases. Two major events (i.e., grade 3 or 4) were confidently classified as unrelated to PRRT: one case of duodenal perforation related to chronic corticoid therapy without proton pump inhibitor coverage; and one case of syncope related to a known cardiac rhythm disorder.

Subacute toxicity of personalized PRRT is presented in Table 6. Fifty (96.2%) and 33 patients (63.5%) experienced subacute toxicity of grade 1 or 2 and of grade 3 or 4 respectively. In only one patient, toxicity was the cause for interruption of the induction course (grade 4 neutropenia after the third cycle). The most common grade 3 or 4 subacute toxicity was lymphocytopenia (51.9%). One patient with extensive bone metastases received an estimated cumulative BM absorbed dose of 4.25 Gy and experienced subacute grade 3 leukopenia and grade 4 lymphocytopenia. Four other patients accumulated more than 2 Gy to the BM and had grade 3 lymphocytopenia. Two of them had bone metastases, of whom one also had grade 3 thrombocytopenia (Supplementary Table 2). It should be noted that the

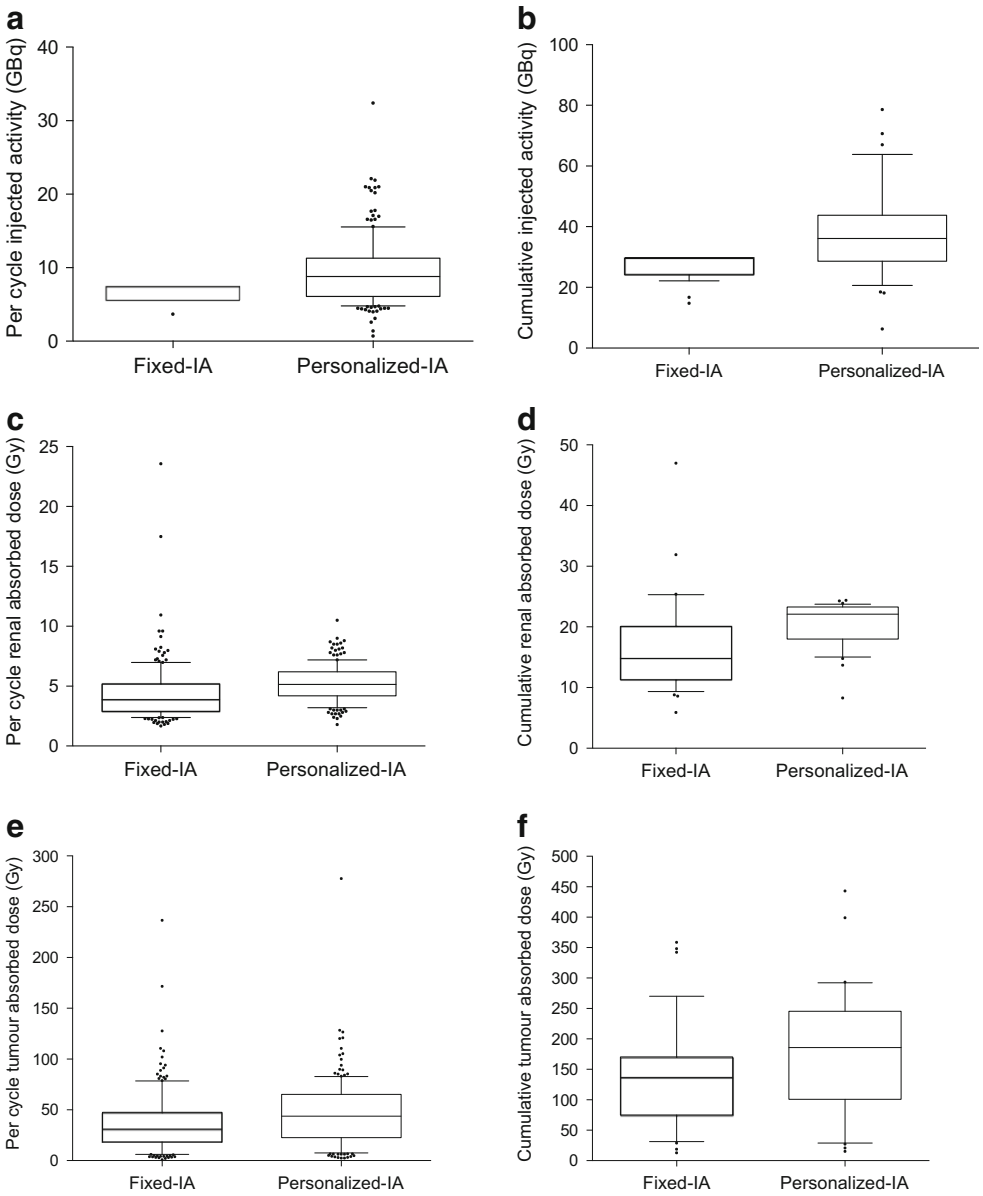


Fig. 1 Comparison between personalized PRRT and simulated empiric, fixed-injected activity (IA) PRRT. The per-cycle (n = 170) and cumulative (during induction course, n = 34) injected activities (**a** and **b** respectively), renal absorbed doses (**c** and **d** respectively) and maximum tumour absorbed doses (**e** and **f** respectively) are compared. *Boxes* represent the interquartile ranges, and *whiskers* the interdecile ranges

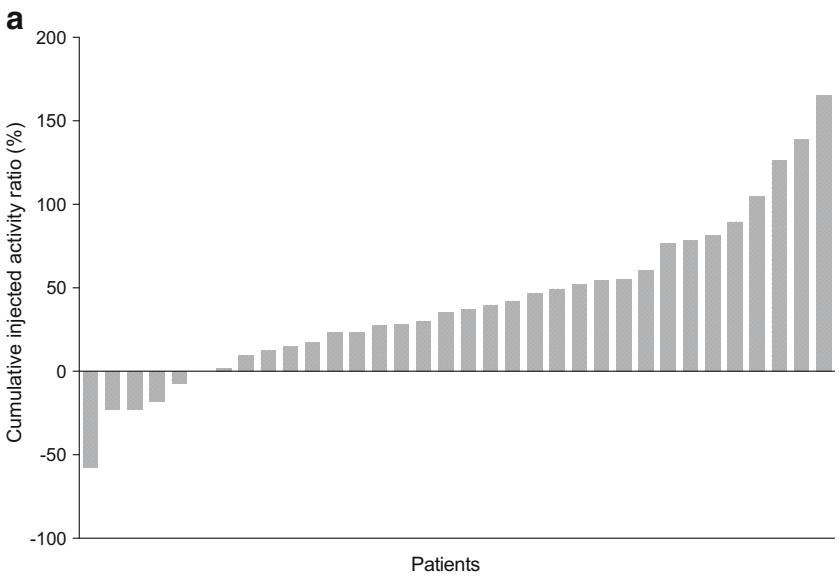
patient who received the highest cumulative IA (76.8 GBq over four induction cycles) experienced no significant subacute BM toxicity (Fig. 5).

In 21 patients assessable for chronic toxicity, one had grade 4 lymphocytopenia, three had grade 3 lymphocytopenia, one had grade 3 anaemia and another one had grade 3 neutropoenia. No patient experienced significant renal toxicity following personalized PRRT (Table 6). Nine months after the first cycle, the patient who received a cumulative IA of 76.8 GBq experienced no chronic renal or BM toxicity of any grade.

Dose–effect and dose–dose relationships

We found a significant, weak inverse correlation between the absolute and the relative platelet count variations evaluated over 6 weeks after each cycle (cycle baseline vs nadir) and the per-cycle BM absorbed dose (Fig. 6). No other significant correlations were found between the subacute or chronic variations of other blood counts and the per-cycle or cumulative BM absorbed doses respectively. No significant correlation was found between the chronic eGFR variation and the cumulative renal absorbed dose. In 11 patients, in 24 measurable NET lesions for which dosimetry was performed, no significant correlation could be evidenced between the radiological size reduction and the cumulative lesion absorbed dose.

Interestingly, we found a significant, positive correlation between the per-cycle renal and BM absorbed doses per IA (Fig. 7a). The strength of this correlation improved by excluding patients with bone metastases (Fig. 7b). A significant correlation was also found between the per-cycle renal and tumour$_{max}$ absorbed doses per IA (Fig. 7c).



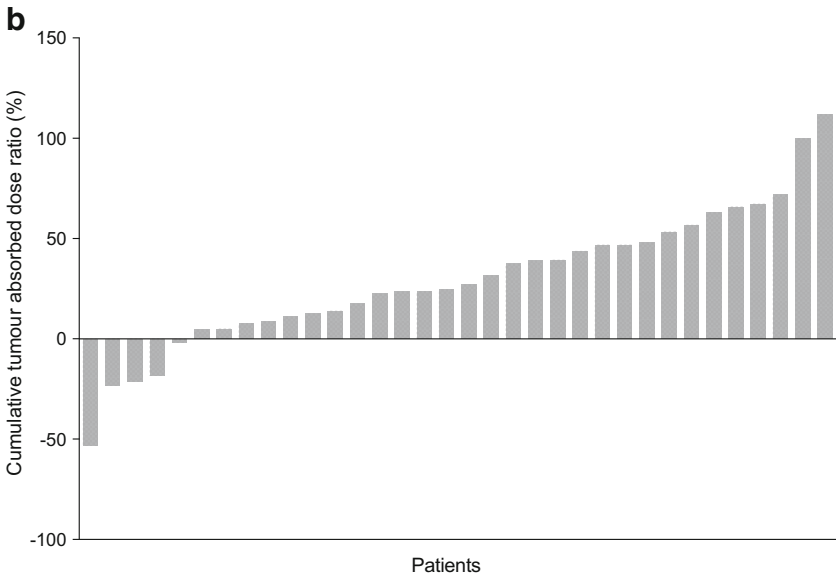


Fig. 2 Cumulative injected activity (**a**) and maximum tumour absorbed dose (**b**) ratios between the personalized and simulated empiric PRRT in patients who completed the induction course ($n = 34$). In 29 patients (85%) , personalized PRRT allowed an increase in the cumulative injected activity and, consequently, the maximum tumour absorbed dose

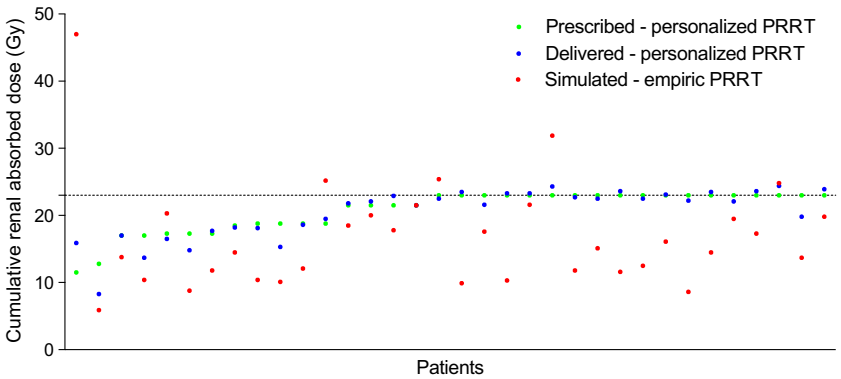


Fig. 3 Prescribed, delivered, and simulated renal absorbed doses in patients who completed the induction course of personalized PRRT ($n = 34$, in ascending order of prescribed dose). In 16 cases, the prescribed renal absorbed dose was less than 23 Gy due to a shortened induction course (four patients received three cycles) or observed dose reductions as per protocol. The renal absorbed dose simulated for the empiric PRRT (7.4 GBq per cycle, to which the same percent activity reduction was applied when appropriate) shows that that 85% (29/34) of patients would have been undertreated under this one-size-fits-all regime, while two patients would have received a renal absorbed dose above 30 Gy

Table 3 Response and survival ($n = 39$)

Patient	Primary tumour	Cycles	Per-induction response	Post-induction response			Time to best response (months)	Follow-up time (months)	Progression-free survival (months)	Overall survival (months)
			^{177}Lu-octreotate QSPECT/CT	Octreoscan/ Ga^{68} PET/CT	RECIST	SWOG				
1	Midgut	2	PD [a]	–	–	–	1.9	2.6	2.6	2.6
2	Esthesioneuroblastoma	4	PR	PD* [b]	PD	PD	1.9	16.9	11.3	–
3	Pancreas	3	MR	MR	PR	MR	8.4	16.6	–	–
4	Unknown	4	SD	–	SD	SD	1.9	13.5	–	–
5	Unknown	4	SD	SD	–	–	2.3	15.9	15.9	15.9
6	Unknown	4	PR	PR	PR	PR	2.3	14.0	–	–
7	Pancreas	3	MR	MR	MR	MR	3.7	9.8	9.8	9.8
8	Midgut	4	SD	SD	SD	SD	2.1	15.0	–	–
9	Pancreas	4	MR	PD* [c]	PD	PD	4.0	15.0	9.2	–
10	Paraganglioma	4	SD	SD	SD	SD	1.9	16.0	–	–
11	Midgut	5 [d]	SD	SD	–	–	1.9	15.1	–	–
12	Midgut	3	MR	–	–	–	1.9	8.3	–	–
13	Lung	2	PD [a]	–	–	–	2.1	8.1	4.2	8.1
14	Pheochromocytoma	4	SD	SD	–	–	2.1	12.4	–	–
15	Pancreas	3	PR	–	–	–	4.4	10.2	10.2	10.2
16	Pheochromocytoma	4	SD	SD	SD	SD	2.3	10.9	–	–
17	Pancreas	4	SD	SD	–	–	2.1	10.4	–	–
18	Colon	4	SD	SD	SD	SD	1.9	9.6	–	–
19	Pancreas	4	MR	MR	–	–	4.0	10.9	–	–
20	Pancreas	4	MR	–	–	–	4.0	10.6	–	–
21	Lung	4	PR	PR	–	–	4.7	9.9	–	–
22	Pancreas	4	PR	PR	MR	MR	4.7	9.5	–	–
23	Midgut	4	MR	–	–	–	6.1	9.4	–	–
24	Midgut	3	PD* [e]	–	–	–	4.2	5.8	4.7	–
25	Midgut	4	MR	–	–	–	3.7	7.7	–	–
26	Midgut	4	SD	SD	–	–	1.9	8.8	–	–
27	Paraganglioma	4	PR	–	–	–	1.9	7.5	–	–
28	Midgut	4	SD	–	–	–	1.6	7.4	–	–
29	Midgut	4	MR	–	–	–	5.8	7.3	–	–
30	Pancreas	4	PR	–	–	–	4.2	7.6	–	–
31	Pancreas	4	MR	–	–	–	4.2	7.4	–	–
32	Midgut	4	MR	–	–	–	6.1	7.0	–	–
33	Pancreas	4	PR	–	–	–	4.0	5.8	–	–
34	Stomach	4	PR	–	–	–	3.7	5.6	–	–
35	Midgut	4	MR	–	–	–	3.7	6.1	–	–
36	Midgut	4	SD	–	–	–	1.9	7.0	–	–
37	Pancreas	4	SD	–	–	–	1.9	6.1	–	–
38	Pancreas	3 [f]	MR	–	–	–	3.7	5.1	–	–
39	Unknown	3 [f]	MR	–	–	–	3.7	3.7	–	–
N			39	17	11	11				
Response: no. (%)										
PR			9 (23.1)	3 (17.6)	2 (18.2)	1 (9.1)				
MR			14 (35.9)	3 (17.6)	2 (18.2)	3 (27.3)				
SD			13 (33.3)	9 (52.9)	5 (45.5)	5 (45.5)				
PD/PD*			3 (7.7)	2 (11.8)	2 (18.2)	2 (18.2)				

Table 3 (continued)

Patient	Primary tumour	Cycles	Per-induction response	Post-induction response			Time to best response (months)	Follow-up time (months)	Progression-free survival (months)	Overall survival (months)
			^{177}Lu-octreotate QSPECT/CT	Octreoscan/ Ga^{68} PET/CT	RECIST	SWOG				
Median (range)							3.7 (1.6–8.4)	9.4 (2.6–16.9)	15.9 (2.6–not reached)	Not reached (2.6–not reached)

PR, partial response; MR, minor response; SD, stable disease; PD, progressive disease; PD*, stability or response of octreotate/octrotide-avid disease but progression/appearance of non-avid lesion(s)

The post-induction molecular imaging and radiological responses were evaluated 3 months after the last induction cycle ($n = 18$)

[a] Patients died from clinical progression and considered PD

[b] Progression of a non-avid lesion 2 months after fourth induction cycle after PR during PRRT

[c] Progression of non-avid liver lesions at the 3-month follow-up after MR during PRRT

[d] Four induction and one maintenance cycles

[e] PRRT interrupted due to the progression of non-avid liver and ovarian lesions

[f] Ongoing induction course

Discussion

The widely adopted empiric PRRT protocol consists in the administration of four induction cycles of a fixed IA of ^{177}Lu-octreotate, such as 7.4 GBq, despite the known very high interindividual variability in absorbed radiation doses per IA to the critical organs, which we demonstrate again here [3–7]. Hence, the one-size-fits-all PRRT regime cannot be considered *standard* from a radiobiological standpoint. On one hand, the very good tolerability of the empiric PRRT regime is consistent with the fact that the vast majority of patients receive absorbed doses lower than the external radiotherapy-derived safety thresholds of 23 Gy to the kidney (and this value is conservative when applied to ^{177}Lu-PRRT [14]), and 2 Gy to the BM. On the other hand, response rates are only moderate and could be improved by increasing tumour irradiation [1, 3]. However, substantially increasing the fixed IA in all patients is not reasonable to achieve this, as severe toxicity rates would eventually rise and PRRT would lose a key advantage over most chemotherapies and biotherapies, i.e., its excellent tolerability. Standardizing absorbed dose to critical organ(s) appears a more promising approach to optimize PRRT. The Uppsala and the Lund groups have suggested varying the number of fixed-IA induction cycles to deliver 23 Gy or 27 Gy to the kidney. In such a protocol, the length of the induction course can vary from as little as 2 months (two 2-monthly cycles) to as long as 18 months (ten 2-monthly cycles) [5, 6]. Instead, we favoured another approach: personalizing IA to deliver a prescribed renal absorbed dose of 23 Gy to the kidney over a fixed number of cycles. While both personalized PRRT approaches can increase the cumulative absorbed dose to the tumour to a similar extent as compared to empiric PRRT, our protocol is the only one that can also increase the tumour absorbed dose per cycle, which has the potential to accelerate and amplify the therapeutic response.

We herein show that it is feasible to accurately control and limit the renal absorbed dose using a practical QSPECT-based dosimetry approach. This made it possible to increase the maximum cumulative $\text{tumour}_{\text{max}}$ absorbed dose by up to 2.12 fold (median, 1.26 fold), as compared with the simulated empiric PRRT regime. These results are similar to those obtained in our simulation study, in which we computed a median 1.37-fold increase of the cumulative $\text{tumour}_{\text{max}}$ absorbed

Table 4 Best response per NET subgroup

	PR: no. (%)	MR: no. (%)	SD: no. (%)	PD: no. (%)
Midgut ($n = 14$)	0 (0.0)	6 (42.9)	6 (42.9)	2 (14.3)
Pancreatic ($n = 13$)	4 (30.8)	7 (53.8)	2 (15.4)	0 (0.0)
Others[a] ($n = 12$)	5 (41.7)	1 (8.3)	5 (41.7)	1 (8.3)
Total ($n = 39$)	9 (23.1)	14 (35.9)	13 (33.3)	3 (7.7)

PR, partial response; MR, minor response; SD, stable disease; PD, progressive disease

[a] Two pheochromocytomas, two paragangliomas, two lung NETs, one stomach NET, one esthesioneuroblastoma, and four NETs of unknown origin

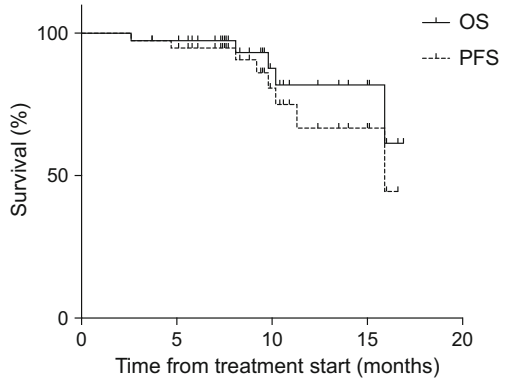


Fig. 4 Progression-free (*PFS*) and overall survival (*OS*) of patients treated with personalized PRRT ($n = 39$). After a median follow-up of 9.4 months, the median PFS was 15.9 months, and the median OS was not reached

dose (range, 0.68–2.64 fold) [7]. Despite increasing the cumulative IA in 85% of subjects and up to 78.6 GBq over four cycles — a level never reported before, to our knowledge — personalized PRRT was associated with a low rate of clinically-relevant toxicity. The rates of severe toxicity other than lymphocytopenia are quite similar to those reported in series of patients treated with empiric ^{177}Lu-octreotate PRRT, with rates of grade 3 or 4 haematological toxicities below 10% and the absence of severe renal impairment [1–4, 7]. Lymphocytopenia of grade 3 or 4 is the exception and appears higher than previously reported for empiric PRRT, including in our own retrospective cohort, but without clinical consequences such as opportunistic infections. This probably reflects the increased systemic and BM irradiation resulting from our protocol.

Our preliminary efficacy results are encouraging, with 59% of patients overall responding (PR + MR) and only 8% progressing as the best response. In patients with pNET, 85% responded; the other 15% had SD. These figures compare favourably with those from the Rotterdam cohort, in which patients receiving empiric PRRT responded (PR + MR) in a proportion of 46% overall, and 64% in the pNET patient subgroup [3]. While we acknowledge that the sample size of our preliminary analysis is limited, and NETs are a heterogeneous group of neoplasms, our results nevertheless point towards increased tumour irradiation (in 85% of our patients, as compared with empiric PRRT) as a likely cause for our enhanced response figures. PFS was 15.9 months but was dependent on only three patients at risk at that timepoint. We observed a significant improvement of GHS/QOL score in 50% of patients, as compared to 36% for the Rotterdam group [11]. Other PRRT optimization strategies have been reported, such as radiosensitization with capecitabine/5-fluorouracil with or without temozolomide, with promising results [15–17]. Intense research aiming at improving SSTR-targeting radiopharmaceuticals is still ongoing, and SSTR antagonists as well as alpha emitters may also further increase the therapeutic index of PRRT [18–20]. Clearly, continuing to refine the personalization of PRRT using improved radiopharmaceuticals in combination with radiosensitizers has the potential to propel PRRT to another level of efficacy and clinical impact.

Unlike industry-sponsored trials such as NETTER-1 in which 3-monthly CT scans are the norm to follow up patients, we could only mandate a reasonable use of medical imaging that is consistent with routine clinical practice. We therefore elected to also use the per-PRRT QSPECT/CT scans to assess the response, in addition to the follow-up imaging routinely prescribed at 3 months after the last induction cycle. We observed a very good concordance between the per-PRRT response and the follow-up molecular imaging and radiological responses in 18 patients. We found that molecular imaging is more convenient for assessing the response of the overall SSTR-positive tumour burden than is anatomical imaging where a limited number of lesions are measured, particularly in patients with widespread disease. Further, molecular imaging better depicts viable bone NET metastases and their response. However, particular attention to progression or appearance of non-avid lesions must be paid to the CT component of (Q)SPECT/CT or ^{68}Ga-PET/CT; and in the case of

Table 5 Acute and subacute side effects

	Acute (< 72 h after cycle onset)		Subacute (< 2 months after cycle onset)	
	Per cycle ($n = 171$)	Per patient ($n = 52$)	Per cycle ($n = 142$)	Per patient ($n = 52$)
Grade 1 or 2				
Nausea	15.8%	32.7%	0.7%	1.9%
Fatigue	1.8%	5.8%	13.4%	30.8%
Abdominal pain	6.4%	17.3%	0.7%	1.9%
Injection-site discomfort	4.1%	11.5%	0%	0%
Vomiting	4.1%	7.7%	0%	0%
Palpitation	1.8%	3.8%	0%	0%
Headache	1.2%	3.8%	0%	0%
Malignant hypertension	1.2%	3.8%	0%	0%
Flushing	1.2%	3.8%	0.7%	1.9%
Radiation dermatitis	0%	0%	0.7%	1.9%
Alopecia	0%	0%	0.7%	1.9%
Dorsal pain	0%	0%	1.4%	3.8%
Dysgeusia	0%	0%	0.7%	1.9%
Melena	0%	0%	0.7%	1.9%
Constipation	0.6%	1.9%	0%	0%
Arterial hypotension	0.6%	1.9%	0%	0%
Hyperglycaemia	0.6%	1.9%	0%	0%
Facial pain	0.6%	1.9%	0%	0%
Lower limb pain	0.6%	1.9%	0%	0%

Table 6 Subacute and chronic haematological and biochemical toxicity

	Subacute (onset < 2 months after cycle)		Chronic (persistence > 2 months after induction course)
	Per cycle ($n = 158$)	Per patient ($n = 52$)	Per patient ($n = 21$)
Grade 1 or 2			
Lymphocytopenia	38.6%	71.2%	57.1%
Leukopenia	30.4%	55.8%	61.9%
Thrombocytopaenia	25.3%	48.1%	47.6%
Anaemia	10.1%	21.2%	38.1%
Worsening of liver function tests	22.2%	36.5%	33.3%
Neutropoenia	14.6%	26.9%	33.3%
Renal impairment	3.2%	5.8%	14.3%
Grade 3 or 4			
Lymphocytopenia	29.7%	51.9%	19.0%
Anaemia	3.2%	7.7%	4.8%
Worsening of liver function tests	3.2%	5.8%	0%
Leukopenia	1.9%	5.8%	0%
Thrombocytopaenia	1.9%	5.8%	0%
Neutropoenia	1.3%	3.8%	4.8%

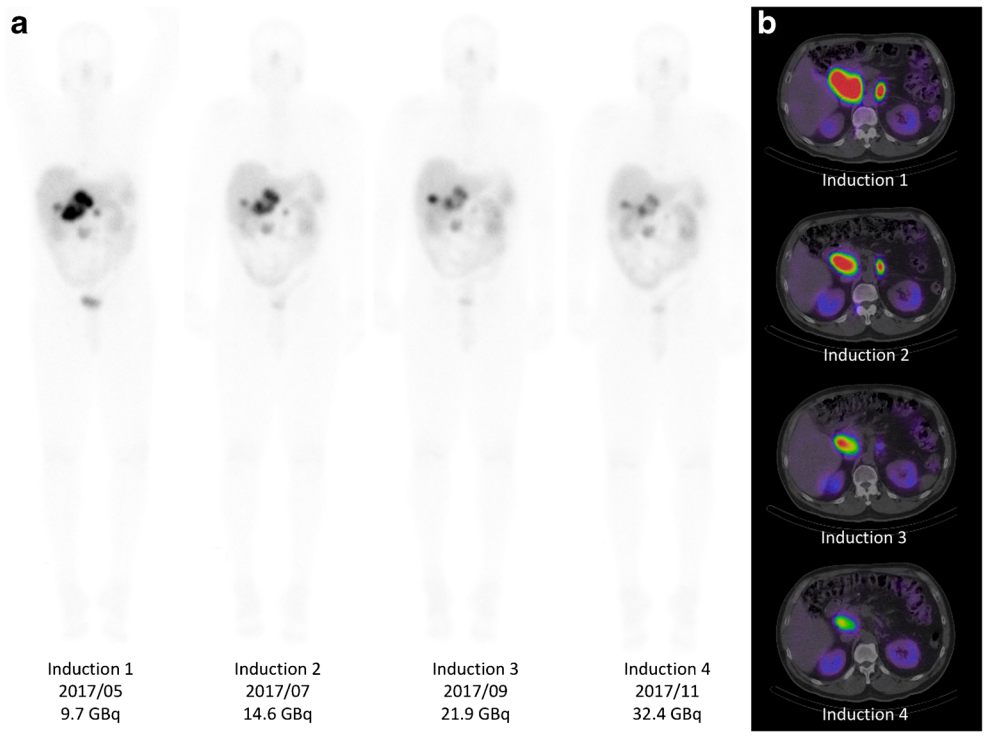


Fig. 5 Personalized ^{177}Lu-octreotate PRRT in a 52-year-old man suffering from a functional paraganglioma, with nodal, liver, and bone metastases. The renal absorbed dose per injected activity was low (0.27 to 0.31 Gy/GBq). The injected activity was thus escalated at each of four induction cycles, yielding a cumulative injected activity of 78.6 GBq, and cumulative absorbed doses of 22.2, 1.2, and up to 98 Gy to the kidney, the bone marrow, and the tumour respectively. He had no significant side-effects or toxicity (only subacute grade 1 leukopenia and grade 2 lymphocytopenia). He had a partial response during the induction course, as seen on the post-treatment whole-body scan (**a**) and selected QSPECT/CT slices (**b**, dominant nodal mass). He also had biochemical and clinical responses, with a greater than 80% reduction in urinary catecholamines, as well as an improvement in the control of his high blood pressure and of his diabetes, with medication reductions

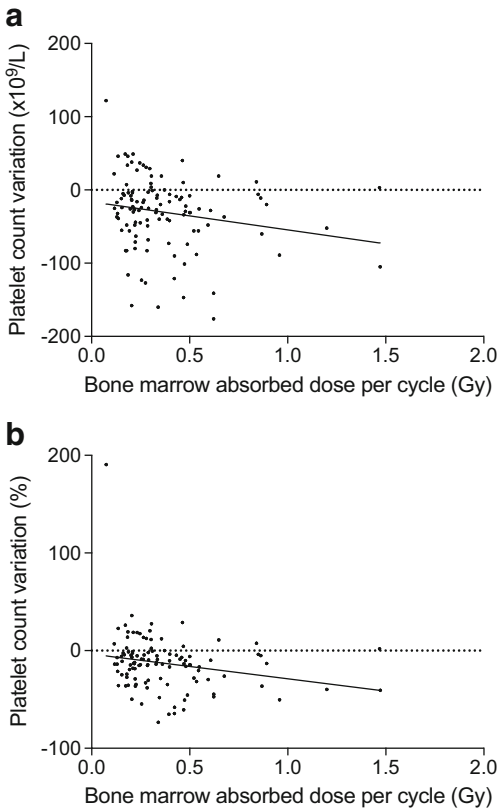


Fig. 6 Per-cycle correlation between the absolute (**a**) or relative (**b**) subacute platelet count variation (up to 6 weeks after cycle onset vs pre-cycle) and the bone marrow absorbed dose (Spearman $r = -0.21$ and -0.23 respectively; $P = 0.03$ and 0.01 respectively; $n = 114$). The *solid lines* represent the linear regressions, for illustrative purposes

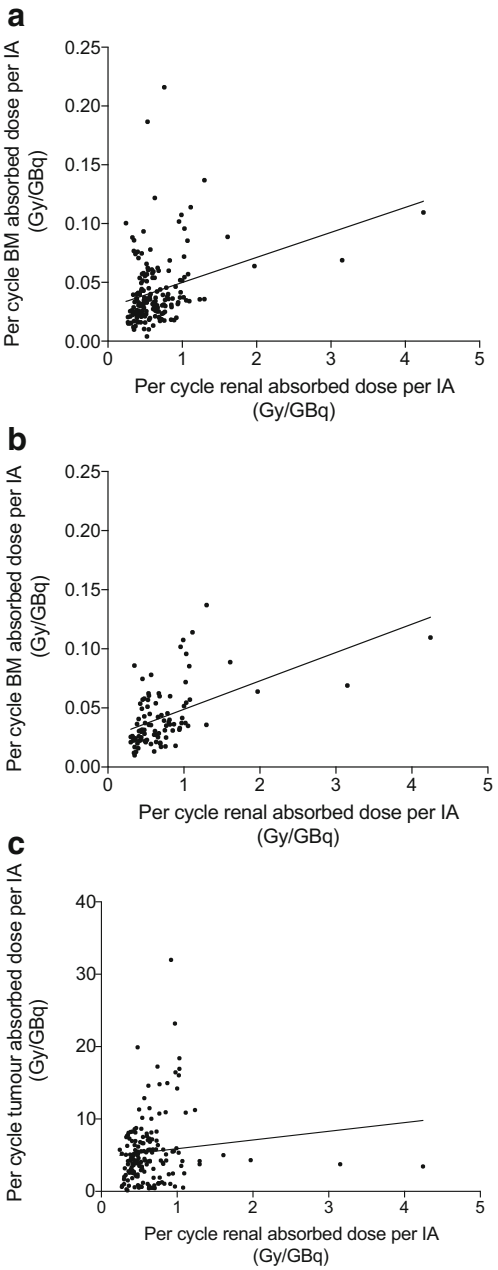


Fig. 7 Correlation between the bone marrow (*BM*), tumour and renal absorbed doses per injected activity (*IA*). **a** There was a significant correlation between the per-cycle BM and renal absorbed doses per IA (Spearman $r = 0.31$, $P < 0.0001$; $n = 170$). **b** When excluding patients with bone metastases, the correlation improved (Spearman $r = 0.50$, $P < 0.0001$; $n = 94$). **c** There was a significant correlation between the per-cycle tumour and renal absorbed doses per injected activity (Spearman $r = 0.16$, $P = 0.04$; $n = 170$). The s*olid lines* represent the linear regressions, for illustrative purposes

equivocal findings, ^{18}F-fluorodeoxyglucose-PET/CT and/or contrast-enhanced CT or MRI may be helpful. By imposing a minimum of 3 months from treatment initiation before classifying response as SD (but not for PD), we believe our response data is fair. Our PR figures could even be underestimated, as we had many cases of early MR and SD with limited follow-up, and it is known that response category may improve over time without further treatment [3].

Our QSPECT dosimetry approach based on three time points at up to 72 h yields absorbed dose estimates per IA that are well within the range of those previously reported using a variety of techniques [5, 6, 21]. We believe that our methods constitute a good trade-off between practicality (as we treat many out-of-city patients) and the achievement of a clinically-relevant level of accuracy that allows reaching our goal of reducing the interpatient renal absorbed dose variability from that of fixed-IA PRRT, which is plagued with an almost 20-fold range (Table 2). While extensive scanning over a longer period of time could potentially improve the accuracy of dosimetry, it has been shown that, for the kidney and the tumour, a respectable accuracy (errors not exceeding 25% in any patients) can be reached by assuming a monoexponential effective activity decay beyond 24 h and scanning only once at 72 or 96 h [22]. We adopted the small-sphere VOI activity concentration sampling for rapidity and convenience in a routine clinical practice setting. Sandström and co-workers previously showed that this approach appears superior to time-consuming full-organ segmentation [23]. Our dosimetry protocol yields reproducible results, and we have now further

simplified it by scanning patients only two times, i.e., at 24 h and 72 h [24]. Differences in dosimetry methods (e.g., planar vs SPECT, number and timing of scans, segmentation vs activity sampling, use of absorbed dose vs biologically effective dose, etc.) can limit comparisons with results from other groups, particularly those who personalize PRRT based on dosimetry [5, 6]. However, we believe that the impact of these methodological differences is relatively minor in the end, as our respective dose estimates per IA are similar, and we all reach the same conclusion that the majority of patients are undertreated with empiric PRRT.

Imaging-based BM dosimetry is challenging, particularly in patients with bone metastases, and we elected not to include BM dosimetry into the PRRT personalization scheme. Nevertheless, our QSPECT-based BM dosimetry methods yielded per-cycle estimates that did correlate with subacute platelet count drop in two independent cohorts [7]. Because the subacute haematological toxicity is associated with an increased occurrence of myelodysplasia and leukaemia [25], we use blood count monitoring as a short-term biomarker of BM tolerance to systemic radiation to further personalize IA.

Because BM absorbed dose is correlated to renal absorbed dose, standardizing the latter indirectly contributes to limiting the former. Further, we also found a positive correlation between the tumour and renal absorbed doses per IA. Altogether, these results are consistent with the fact that a faster biological clearance of the ^{177}Lu-octreotate, because of a good renal function and other individual factors, results in lower absorbed doses to both tumour and critical organs, further supporting increasing IA in patients who can afford it.

In conclusion, the preliminary results of our ongoing prospective study of personalized PRRT, the P-PRRT trial, confirm the feasibility of delivering a prescribed renal dose by personalizing the injected activity based on dosimetry. This approach appears safe and allows to significantly increase tumour irradiation. Our initial efficacy results are suggestive of enhanced therapeutic response, particularly in patients with pancreatic NET, as well as a positive impact on the quality of life.

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Compliance with ethical standards

Conflicts of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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