Journal of Nuclear Medicine, published on November 27, 2020 as doi:10.2967/jnumed.120.252494

A rapid and safe infusion protocol for lutetium-177 peptide receptor radionuclide therapy

Sander C. Ebbers[1], Maarten W. Barentsz[2], Bart de Keizer[1], Gerard C. Krijger[1], Marnix G.E.H. Lam[1], Arthur J.A.T. Braat[1]

[1] Department of Nuclear Medicine, University Medical Center Utrecht

[2] Department of Radiology, University Medical Center Utrecht

21 August, 2020

Correspondence: s.c.ebbers-2@umcutrecht.nl Departments of Radiology and Nuclear Medicine, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands

Word count:
Abstract: 288
Manuscript: 3757

Short running title: Rapid infusion in PRRT

ABSTRACT

Purpose

Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-labelled somatostatin analogues in patients with somatostatin-receptor expressing tumors is often performed using administration protocols prescribing a 30 minutes infusion time. The most often used method of infusion is the gravity method, by which the complete dose is effectively administered exponentially. However, there is no evidence to explicitly support an infusion time of 30 minutes. This study aims to investigate the safety of an infusion time of less than 5 minutes.

Methods

A cohort study was performed, examining the biochemical and clinical toxicity after PRRT when using a fast infusion protocol with a maximum infusion time of 5 minutes. Data on patient characteristics, laboratory tests, follow-up visits and pre- and post-treatment imaging using ^{68}Ga-DOTA-TOC PET/CT from patients treated with PRRT at the University Medical Center Utrecht (UMC Utrecht) were collected. All patients receiving PRRT using the fast-infusion protocol were included. If no laboratory or clinical follow-up was available, patients were excluded. In addition, a laboratory experiment was performed, simulating the standard-infusion protocol using the gravity method.

Results

31 patients were included, who were treated using the fast infusion protocol. Clinical toxicity mainly consisted of grade 1/2 fatigue (87.1%) and grade 1 nausea and/or vomiting (67.7%) during follow-up. No acute or long term clinical toxicity possibly related to the fast infusion protocol was reported. Grade 3/4 hematological toxicity occurred after PRRT in one patient (3.2%). No grade 3/4 renal toxicity occurred. The laboratory experiment showed that when using the gravity method for infusion, half of the activity is infused after 3.5 minutes, and 95% is infused within 15 minutes.

Conclusion

A faster infusion of PRRT using an infusion time of less than 5 minutes is safe and feasible in clinical practice.

KEYWORDS

Peptide receptor radionuclide therapy; infusion protocol; ^{177}Lu-DOTA-TATE; fast infusion

BACKGROUND

Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTA-TATE/DOTA-TOC/HA-DOTA-TATE is increasingly being used for treatment of inoperable grade I/II neuroendocrine neoplasms (NEN) (*1*–*4*). PRRT uses the radioactive isotope ^{177}Lu, coupled to a peptide that mainly targets somatostatin subtype 2 receptors (SSTR2). These receptors are often highly overexpressed on the cell surface of NENs and some other type of tumors (*5*,*6*). The radiopharmaceutical binds to the receptor with high affinity and is internalized by the tumor cells after intravenous administration. The presence of the SSTR2 receptors can easily be made visible by gallium-68-somatostatin receptor positron emission tomography/computed tomography (^{68}Ga-SSTR PET/CT) (*7*). The treatment is safe, as toxicity is limited to grade I-II hematotoxicity in less than 10% of patients and is often transient (*3*,*8*,*9*). Grade III or IV hematotoxicity or a decreased renal function rarely occur after treatment with PRRT. When PRRT is administered, multiple precautionary measures are taken to ensure a safe infusion for the patient as well as the health care personnel performing the administration (*10*,*11*). According to the instructions from the manufacturer of ^{177}Lu-DOTA-TATE (Lutathera®, Advanced Accelerator Applications, Novartis, Saint Genis Pouilly, France), the prescribed method of administration is the so-called gravity method. This method utilizes gravity to flush the vial containing the radiopharmaceutical with 0.9 mg/mL saline solution for injection, while regulating the flow to a specific infusion rate. The instructed duration of the infusion is 30 minutes, during which a constant flow of 400 mL/h should be maintained. The infusion time was set to be 30 minutes when the first results on patients treated with PRRT were published, and all subsequently published protocols adapted this 30-minute infusion time (*1*,*12*). However, other administration methods are considered, often utilizing a pump to ensure a more constant infusion in PRRT (*13*,*14*). By using a pump, a faster infusion time can be achieved. However, there are concerns when infusing at a faster rate, due to the lack of safety studies. In the current study, we investigate the

safety of a faster infusion in PRRT by analyzing toxicity profiles after PRRT using the fast-infusion protocol, in which a total intravenous infusion time of 5 minutes is used.

METHODS

Patients

All patients treated with PRRT (in-house labelled ^{177}Lu-HA-DOTATATE, Scintomics, Germany) using the fast-infusion protocol (regular care in our hospital since March 2017) from September 2016 until April 2019 were included. ^{177}Lu-HA-DOTA-TATE was prepared in house using a semi-automated Modular-Lab eazy synthesis module (Eckert & Ziegler, Berlin, Germany). Each synthesis was performed according to the manufacturers' instructions using a prefabricated cassette, a GMP-grade ascorbic acid buffer, a C18 cartridge and a 0.22 µm pore size sterilization filter. An amount of 50 µg HA-DOTA-TATE (Scintomics) per GBq 177Lu (EndolucinBeta, ITM Medical Isotopes GmbH, Garching, Germany) was used. The pH of the batches ^{177}Lu-HA-DOTA-TATE was 4.7 (4.2-5.2). Per patient the batch was diluted with 0.9% NaCl to 8 mL for infusion of 7.4 GBq 177Lu-HA-DOTATATE with an osmolality of 272-287 mOsm/kg.

Treatment indications for all patients were discussed in a multidisciplinary tumor board. The European Association of Nuclear Medicine guidelines were followed to include patients for treatment (*15*). All patients had sufficient somatostatin-receptor expression on ^{68}Ga-DOTA-TOC/HA-DOTA-TATE PET/CT (i.e. more than healthy liver tissue) and had an inoperable NEN or other type of tumor for which there was no other treatment option. Patients who received at least one cycle of PRRT were included. Patients were excluded if laboratory investigations on hepatic, hematologic, and renal function before or after treatment were not available. As this is a retrospective study, the need for approval of the study protocol and informed consent by the included patients was waived.

Study Procedures

Patients were screened by the nuclear medicine physician. Complaints and physical examination were recorded at baseline and laboratory investigations were performed (i.e. renal function, hepatic function and enzymes, and hematologic status). Baseline toxicity was recorded. Patients were admitted

to the radiation ward on the day of administration. Preparation consisted of new laboratory investigations, a single dose of 8 mg ondansetron intravenously 30 minutes prior to administration, and co-infusion of an amino-acid solution (1 liter arginine/lysine 2.5%/2.5%). After treatment, patients were discharged from the hospital according to local radiation safety regulations. A control visit was planned four to six weeks after PRRT. If patients received more than one treatment cycle, treatment intervals were in between six and nine weeks.

Administration Method

A commercially available shielded administration pump (RAD-INJECT; Tema Sinergie, Faenza, Italy) was used to provide a constant flow during infusion, with a fixed volume of 12 ml. A shielded syringe with the radiopharmaceutical was loaded into the pump, and connected to a side port of the infusion system used for amino-acid co-infusion. Directly after infusion, the pump extracted a fixed volume from a bag of regular saline solution and flushed the entire system twice to administer any possible remnant of the radiopharmaceutical. A fast infusion time of five minutes was used (including flushing of the system twice; actual radiopharmaceutical infusion in 1.5 minutes). During infusion, patients were closely monitored for any complaints or adverse effects.

Outcomes

Toxicity

The primary outcome of this study was the occurrence of adverse events during or after administration of PRRT. Clinical and laboratory related adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (*16*). Adverse events were only reported if the grade was higher than at baseline. Clinical toxicity was recorded at the day of each treatment cycle and during each follow-up visit four to six weeks after each treatment cycle. Laboratory

investigations were obtained during follow-up visits after each treatment cycle and regularly after completion of PRRT up until one year after the first cycle.

Response

As a secondary outcome, objective response was evaluated after treatment using ^{68}Ga-DOTA-TOC PET/CT imaging. Response was only evaluated in included patients of whom ^{68}Ga-DOTA-TOC PET/CT imaging was available at baseline and after PRRT. Volumes-of-interest (VOI's) were drawn semi-automatically using Syngo.Via (Siemens), based on the recommendations adapted from the PERCIST guidelines (*17*). Regions with high uptake of ^{68}Ga-DOTA-TOC were segmented automatically using a threshold based on a spherical VOI which was placed in the healthy liver tissue. Tissue with physiological SSTR-expression was manually removed from the resulting delineation (i.e. kidneys, bladder, spleen, pituitary gland, adrenals and small intestine). Based on the final VOI's the peak standardized uptake value (SUV_{peak}, corrected for lean body mass), total lesion somatostatin receptor expression (TL-SSTR, derived from total lesion glucolysis (TLG)), and somatostatin receptor expressing tumor volume (SSTR-TV, derived from metabolic tumor volume (MTV)) were calculated. SUV_{peak}, TL-SSTR and SSTR-TV calculated from the baseline and follow-up PET/CT were compared, to assess the response in patients. According to PERCIST guidelines, a threshold of 30% decrease or increase in SUV_{peak} was used to categorize patients as partial metabolic response (PMR), stable metabolic disease (SMD) or progressive metabolic disease (PMD).

Laboratory Experiment

In order to assess the flow of the radiopharmaceutical with the gravity method, the set-up for administration was simulated in our nuclear laboratory at UMC Utrecht (Figure 1). In four subsequent infusion simulation experiments, a glass vial sealed with a rubber septum was filled with technetium-99m pertechnetate ($^{99m}TcO_4^-$) in variable amounts of saline solution (0.9% sodium chloride in water). A

normal saline 0.9% sodium chloride 250 mL bag for injection was connected to the vial via a regular infusion line and a short 19 Gauge (G) needle that was placed through the septum of the vial (the afferent system). A long 20G needle was also placed through the septum with the tip of the needle at the bottom of the vial, and connected to an infusion line, leading towards a waste container for radioactive material (the efferent system). An infusion pump was connected to the efferent line in order to accurately control the flow. The pump was set to pump 200 mL at a rate of 400 mL/h, resulting in an infusion time of exactly 30 minutes. The vial containing the $^{99m}TcO_4^-$ solution was placed in a dose-calibrator, after which injection was initiated. The amount of radioactivity was denoted every 60 seconds, starting at t=0 minutes until t=30 minutes. The measured activity was corrected for background radiation and physical decay. The activity was plotted as a fraction of the total activity against the infusion time. Because this setup essentially is a continuous dilution of the contents of the vial, an exponential depletion curve was fitted to the data using non-linear regression and compared to the observed data. The formula used for exponential depletion was $A_t = A_0 * e^{-\lambda * time}$, where A_0 was the activity fraction in the vial at the start of the infusion (i.e. 100%), λ was the decay constant and $time$ was the time since start of infusion in minutes.

Statistical Analysis

Trends in laboratory findings (i.e. bilirubin, creatinine, thrombocytes, and leukocytes) were examined using linear mixed models. To model the correlation of longitudinal data, an autoregressive correlation model was used. Furthermore, a random intercept and random effect of time on laboratory results were implemented. The models were checked on normality of the residuals. All statistical analysis was done using R (version 3.6.2). P-values of < 0.05 were considered statistically significant.

RESULTS

Clinical Toxicity

A total of *31* patients were included, who received a total of 99 cycles (Table 1). Patients did not report any acute toxicities during or directly after administration. Patients reported multiple CTCAE adverse events, ranging from grade 1 to grade 3 (Table 2). Most patients complained of grade 1 or 2 fatigue, which frequently occurred in the weeks following the administration (27/31 (87.1%)). Other commonly reported adverse reactions were grade 1 or 2 nausea and/or vomiting (21/31 (67.7%)). Two grade 3 adverse events occurred in two patients. The first patient suffered from extreme fatigue after receiving one cycle of PRRT. The fatigue caused further treatment with PRRT to be postponed and eventually be canceled due to worsening of the clinical condition of the patient. Laboratory findings did not reveal a specific cause for the fatigue. The second patient had pre-existing major carcinoid related complaints (flushing and diarrhea, both >10 times a day) and suffered from a carcinoid crisis hours after the first treatment cycle. One day after administration, the patient reported increasing complaints of flushing, diarrhea, cardiac arrhythmias, and dyspnea, despite being adequately treated with short-acting octreotide. Being hemodynamically stable with a normal blood pressure and heart rate, the patient was hospitalized and received a bolus dose of 500 µg of octreotide, as well as continuously intravenous octreotide at 50 µg/h. Over the course of a couple of days, the symptoms reduced and octreotide infusion was stopped. During subsequent PRRT administrations additional care was taken to prevent the occurrence of a carcinoid crisis by preemptive intravenous administration of octreotide 24 hours after PRRT. The patient completed all four treatment cycles of PRRT.

Clear trends of decreasing thrombocyte, leukocyte, and hemoglobin levels were found following PRRT (Figure 2; $p < 0.001$, $p < 0.001$, $p = 0.002$), however, no significant change over time in creatinine levels was observed ($p = 0.267$). In terms of CTCAE grading, grade 1 or 2 hematologic toxicity occurred in

21 (67.7%) of patients (Table 3). Grade 3 hematologic toxicity occurred only once in a patient with thrombocytopenia, which resolved completely after a few months. Grade 1 or 2 renal toxicity occurred in 4 (12.9%) patients treated using the fast infusion protocol. No grade 4 or 5 toxicity was observed in the study period.

Objective Response

Objective response using ^{68}Ga-DOTA-TOC PET/CT imaging was measured in 22 patients, of whom imaging was available at baseline and after PRRT (Table 1). In 9 patients, ^{68}Ga-DOTA-TOC PET/CT imaging was not available after treatment. Based on SUV_{peak} values, PMR was achieved in 12 (54.5%), SMD in 8 (36.4%), and PMD in 2 (9.1%) patients. Median decrease in SUV_{peak} was 31.4% (IQR 11.7% - 62.8%), while median decrease in TL-SSTR and SSTR-TV was 66.5% (IQR 42.2% - 82.8%) and 66.7% (IQR 28.8% - 79.3%), respectively (Figure 3). In three patients in whom a complete reduction in SUV_{peak} was calculated, there was still viable tumor visible on ^{68}Ga-DOTA-TOC PET/CT, which, however, was too little to be included in the automatically delineated VOI's. Therefore, these patients were classified as partial response, rather than complete response (Figure 3).

Laboratory Experiment

A total of *4* vials that contained *709*, *398.9*, *289* and *320.8* MBq of ^{99m}Tc in *23*, *20*, *23* and *21.5* mL of saline solution were flushed using the gravity method, respectively (Figure 4). In vial #1, the observed line deviates from the supposed 'ideal' decay-curve at approximately 8 minutes. This was explained by leakage of air from the vial through the septum, causing the vial to contain more fluid after a certain period. In all other vials, the dilution process followed the exponential decay-curve. The median estimated decay constant was *0.2477* (range *0.1891* - *0.3224*). The median time until 50% of the radioactivity was infused was *3.5* minutes (range *3* - *4* minutes), for 75% *6.5* minutes (range *5* - *8* minutes), and for 95% *15* minutes (range *10* - *29* minutes).

DISCUSSION

In the current study we have shown that it is safe to administer PRRT in a timespan of at least 5 minutes (this includes flushing the administration system twice, thus infusing the radiopharmaceutical in only 1.5 minutes). No additional toxicity was observed, and response rates according to ^{68}Ga-DOTA-TOC PET/CT scans were good. The added benefit of using the gravity method for administering PRRT is questionable, as the laboratory experiment showed that with the gravity method 95% of the dose is administered in 15 minutes, and 50% in 3½ minutes.

The current study shows that a total infusion time of 5 minutes (including thorough flushing of the system) with a constant infusion rate is safe. In terms of clinical and biochemical toxicity, no additional occurrence of adverse events was found. The toxicity profiles in this study are similar to previous reported studies. Brabander et al. (2017) published a cohort of 582 patients, in which grade 3 or 4 combined hematologic toxicity (thrombocytopenia, leukopenia and anemia) was observed in 10% of patients (*18*). In the NETTER-1 trial, grade 3/4 thrombocytopenia occurred in 2% of patients, grade 3/4 leukopenia occurred in 1% of patients, and grade 3/4 anemia was not seen after PRRT. In the current study, overall hematologic toxicity was quite similar (3.2% of patients, due to thrombocytopenia). There was no grade 3/4 anemia or leukopenia in the current study population. However, Brabander et al. reported grade 3/4 lymphocytopenia after PRRT in 50% of patients, while the NETTER-1 trial reported the same in 9% of patients. In the current study, lymphocyte counts were not analyzed, as it was not measured regularly in all patients. As observed in both mentioned studies by Brabander et al. and the NETTER-1 investigators, renal toxicity after PRRT is rare, most importantly due to the combined infusion of an amino-acid solution during treatment. Grade 3/4 renal toxicity is generally reported in 1% of treated patients, but in our cohort, no patients had grade 3 or 4 renal toxicity. Therefore, and considering the infusion curve of the 30 minute protocol, a fast infusion of PRRT has probably no effect on renal toxicity. Furthermore, the occurrence of clinically reported adverse events was comparable to

the rates reported in previously published studies, and no specific complaints were reported by any patient during the infusion of the radiopharmaceutical (*3*,*18*). The NETTER-1 study reported significantly increased nausea and vomiting after PRRT compared to standard SSA (somatostatin analogue) treatment, with rates of 59% for nausea and 47% for vomiting. In the current study, nausea or vomiting occurred in 67.7% of patients (grade 1/2). The most frequently encountered complaint in this study was the occurrence of grade 1 or 2 fatigue, which is often pre-existent, but worsening during treatment. Although (worsened) fatigue during PRRT is commonly described in different cohorts, in the long term a decrease in fatigue is often observed. In the NETTER-1 trial, the hazard for the time-to-deterioration of fatigue was significantly lower in patients treated with PRRT than in patients treated only with SSA (*9*). The relatively high occurrence of fatigue in this study can be explained by the high frequency check-ups, where every mention of fatigue is counted as an adverse event (i.e. before treatment, during each treatment cycle, and after each treatment cycle).

Response after PRRT is usually measured using contrast-enhanced CT or MRI (*2*). Due to the retrospective nature of this study, follow-up imaging using contrast-enhanced CT or MR imaging was not feasible. Therefore, comparison with literature may be difficult. However, in clinical practice, ^{68}Ga-DOTA-TOC imaging is increasingly being utilized during follow-up, especially in low-grade NEN. In our study, response rates after PRRT based on ^{68}Ga-DOTA-TOC PET/CT imaging were rather good, with a partial response rate of 54.5%, and stable disease in 36.4% of patients. Progressive disease was seen in 9.1% of patients.

There are many suggested techniques for safe infusion in PRRT (*19*). The gravity method is the first and most widely implemented technique due to the adaptation after the first clinical trials. An advantage of this method is that no manipulation of the content of the vial is necessary, and only basic materials are necessary for the entire set-up. On the other hand, there can be problems leading to

incomplete infusion of the radiopharmaceutical, such as air-leakage from the vial due to incorrect placement of the needles or defects in the vial's septum. This occurred in 1/4 of our attempts of the laboratory experiment, resulting in a slower infusion of the radiopharmaceutical and potentially higher residual activity. Therefore, the time until complete infusion may vary, even with the same amount of saline solution and configured infusion rate. Additionally, there is risk of contamination due to leakage of radioactivity from the vial (*15*). Apart from these disadvantages, the infused concentration of the radiopharmaceutical is not constant due to the flushing with regular saline fluid. This results in infusion of the vast majority of the activity within the first minutes following initiation of infusion, as shown in the laboratory experiment. Therefore, administration using the flushing (gravity) method essentially equates to infusing the majority of the initial dose in five minutes.

A second technique requires the use of a syringe pump (or IV pump system), into which the radiopharmaceutical solution has been aspirated before treatment (*11*). A similar method was also used in this study. Main advantages of implementing this technique is that there is no risk of air aspiration, and, in our case, flushing of the entire system is also automated, limiting radiation exposure to personnel. Furthermore, the infusion rate is constant. Disadvantages are that equipment should be shielded, and that the radiopharmaceutical has to be handled by laboratory technicians in order to prefill the shielded syringe.

In theory, slow infusion of the radiopharmaceutical exposes the somatostatin receptors on the tumor cells to the compound for a longer period of time, hypothetically increasing the uptake. As a result, shortening the infusion could negatively affect the efficacy of PRRT. However, a shorter infusion time will likewise result in a higher blood concentration, which in turn potentially increases the saturation of somatostatin receptors (*7*). Internalization of these highly saturated receptors would then result in a higher absorbed dose in the tumor cells. Longer infusion of the radiopharmaceutical is only

useful in order to bind to recycled somatostatin receptors, which is a process that is shown to complete only after 24 hours (*20*,*21*). Hence, utilizing the recycled somatostatin receptors for treatment would require much longer infusion times. This is undesirable, as a longer infusion time presents added risks in terms of leakage, extravasation and radiation exposure, and is increasingly uncomfortable to the patient. In addition, the ^{177}Lu decays to some extent. The exact influence of the administration method of somatostatin analogs on the binding and internalization process is still unclear. There are suggestions that a higher concentration of somatostatin analog within a short period of time results in a higher tumor absorbed dose. This is shown by Braat et al. (2019) in a patient with meningioma receiving ^{177}Lu-HA-DOTA-TATE both intravenously and intra-arterially (*22*). Intra-arterial infusion in the feeding artery of the tumor resulted in a very high local blood concentration of the radiopharmaceutical. Comparing both administration methods, an eleven-fold increase in tumor uptake was quantified on the post-treatment ^{177}Lu planar scintigraphy after intra-arterial administration. Another reason to shorten the infusion time is the fact that the agonist-induced desensitization and internalization process is very quick and happens within minutes. Binding of the somatostatin-analog is arguably the most significant within these first minutes.

Faster infusion may also impact the workflow of clinical personnel positively. During infusion, careful monitoring of the process is warranted, thus limiting the amount of patients that can be treated simultaneously, depending on the local procedural guidelines. With a shorter infusion time, a more efficient workflow may be possible.

In our study, there are some limitations. First, long-term clinical toxicity was not investigated. However, after fast infusion of PRRT, mainly short term adverse reactions are of concern. Long-term negative effects of a fast infusion in PRRT are not expected. Secondly, lymphocyte count was not investigated, as data was not sufficiently available. In previous studies a temporary lymphopenia

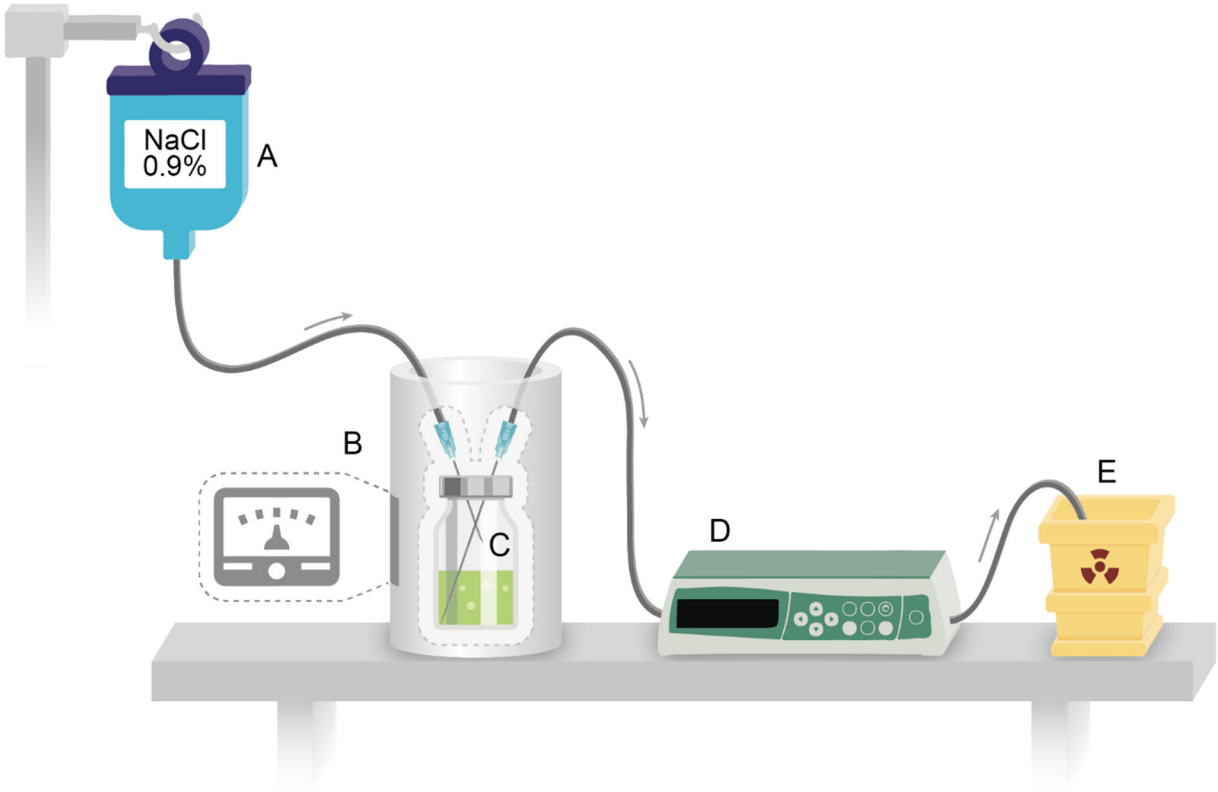
occurred frequently. Thirdly, response after PRRT was measured using ^{68}Ga-DOTA-TOC PET/CT. Even though this imaging technique is a promising tool in the follow-up of PRRT-treated patients, no evidence exists on its validity. In nine patients, PET/CT's were not available for response assessment. In eight patients, follow-up consisted of conventional imaging (i.e. contrast enhanced CT/MRI), and in one patient the image quality of the PET/CT was insufficient to analyze the response. Fourthly, the study population is heterogeneous, as any type of tumor was included. However, as the aim of the study was toxicity after fast infusion of PRRT, this does not affect the validity of the study. Lastly, specific characteristics of different radiopharmaceuticals, such as pH, could in theory have an effect on complaints observed by the patient. In this study, these factors could not be taken into account because only one radiopharmaceutical was used.

As our study is a cohort study, no direct comparison can be made with PRRT using the standard 30-minute protocol. In the future, a randomized controlled trial could be performed comparing both infusion protocols to establish final certainty on the most adequate method of infusion in PRRT. Both the effect on toxicity and on response should be investigated, as the effect of fast infusion on the saturation of somatostatin receptors is still unclear.

In conclusion, rapid administration of PRRT in 5 minutes is feasible and can be safely used in standard clinical practice.

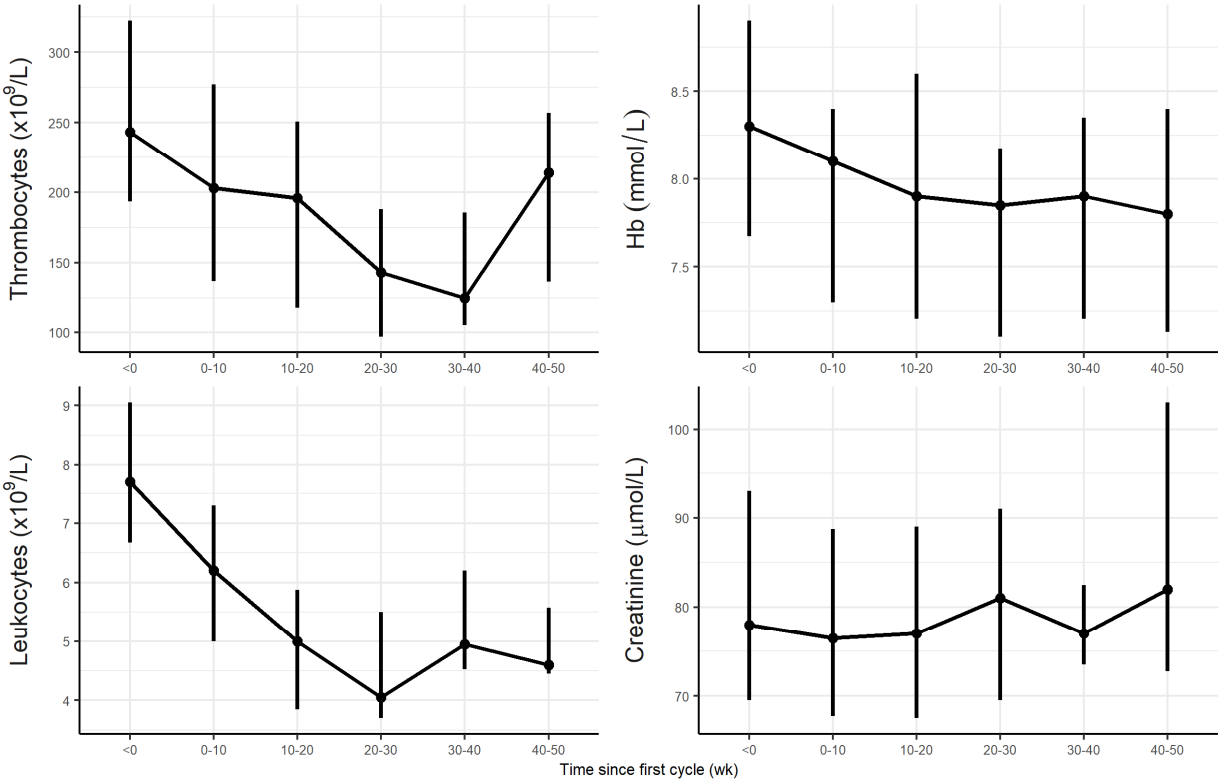
FIGURES

Figure 1. Schematic of the laboratory experiment setup



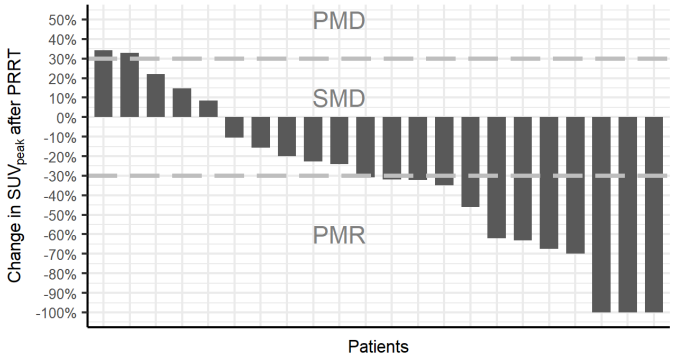
A: Bag of 0.9% saline solution; B: Dose calibrator; C: Vial with dissolved ^{99m}Tc, into which a long and a short needle are inserted; D: Regular infusion pump; E: Radioactive waste container

Figure 2. Several laboratory trends in the 50 weeks after the first cycle of PRRT



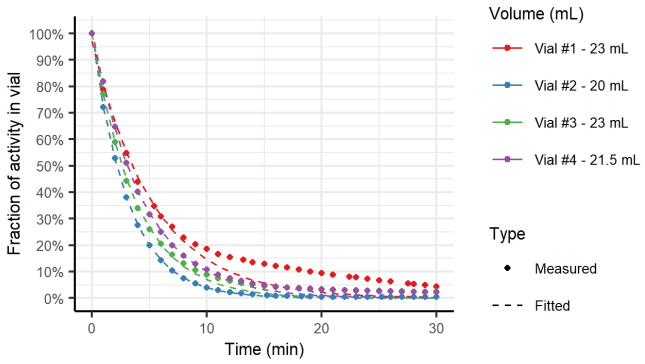
Trends indicate the median level among patients in the indicated time period. Error bars indicate the interquartile range.

Figure 3. Response by SUV_{peak} on ^{68}Ga-DOTA-TOC PET/CT after PRRT



Value at post-PRRT indicate the best response if multiple scans after PRRT were analyzed.

Figure 4. Flow of technetion-99m by the flushing (gravity) method



The measured fraction of the activity remaining in the vial at the time since start of the infusion per vial (dots) and their corresponding fitted decay curves (dashed lines). Note the deviation from the fitted curve in Vial #1 at approximately 8 minutes of infusion time.

TABLES

Table 1. Baseline characteristics

	All patients - N (%)	PERCIST analysis - N (%)
Number of patients	31	22
Number of PRRT cycles	99	76
Age - Median (IQR)	67 (58.5 - 72.5)	67.5 (59.5 - 73.75)
Female	14 (45%)	11 (50%)
Type of tumor		
NEN	23 (74%)	17 (77%)
Type of NEN		
Small bowel	10 (43%)	8 (47%)
Pancreas	5 (22%)	3 (18%)
Colon	2 (9%)	2 (12%)
Gastrinoma	2 (9%)	1 (6%)
Insulinoma	2 (9%)	2 (12%)
Stomach	1 (4%)	1 (6%)
Unknown	1 (4%)	0
Functional NEN	8 (35%)	5 (29%)
SSA treatment	20 (87%)	15 (88%)
Paraganglioma	3 (10%)	2 (9%)
Meningioma	2 (6%)	1 (9%)
Esthesioneuroblastoma	1 (3%)	1 (5%)
Feochromocytoma	1 (3	1 (5%)
Pituitary adenoma	1 (3%)	0
Number of cycles		
1	3 (10%)	1 (5%)
2	7 (23%)	4 (18%)
3	2 (6%)	1 (5%)
4	19 (61%)	16 (72%)
Cumulative dose (GBq) - Median (IQR)	21.62 (14.86 - 21.94)	21.66 (21.32 - 21.91)

Table 2. Clinical toxicity

	Grade 1/2	Grade 3
Fatigue	27(87%)	1 (3%)
Pain	9 (29%)	0 (0%)
Nausea vomiting	21 (68%)	0 (0%)
Xerostomia	1 (3%)	0 (0%)
Anorexia	7 (23%)	0 (0%)
Stomach complaints	4 (13%)	0 (0%)
Abdominal discomfort	3 (10%)	0 (0%)
Diarrhea	5 (16%)	0 (0%)
Flushing	1 (3%)	0 (0%)
Other	22 (71%)	1 (3%)*
Injection site	1 (3%)	0 (0%)

* One patient suffered from a carcinoid crisis shortly after his first treatment cycle. The carcinoid crisis was treated adequately with continuous infusion of short-acting octreotide, with no residual side-effects.

Table 3. Biochemical toxicity

Toxicity	Grade 1/2	Grade 3
Creatinine	4 (13%)	0
Hemoglobine	16 (52%)	0
Leukocyte count	15 (48%)	0
Thrombocyte count	14 (45%)	1 (3%)

KEY POINTS

QUESTION: Is it safe to administer PRRT with an infusion time of five minutes?

PERTINENT FINDINGS: In a cohort study, where patients with NET were treated with PRRT using a fast-infusion protocol, no related clinical or biochemical toxicity was found. Unrelated toxicity profiles are similar to regular PRRT infusion, with grade 1/2 fatigue (87.1%) and grade 1 nausea and/or vomiting (67.7%) being the most frequent, and grade 3/4 hematologic toxicity occurring in one patient (3.2%).

IMPLICATIONS FOR PATIENT CARE: A faster infusion of PRRT is less time-consuming for patients and health care professionals, with no added risk compared to other infusion protocols.

REFERENCES

1. Kwekkeboom DJ, Krenning EP, Lebtahi R, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: Peptide receptor radionuclide therapy with radiolabeled somatostatin analogs. *Neuroendocrinology*. 2009;90:220-226.
2. Pavel M, O'Toole D, Costa F, et al. ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology*. 2016;103:172-185.
3. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of 177 Lu-dotatate for midgut neuroendocrine tumors. *N Engl J Med*. 2017;376:125-135.
4. Baum RP, Kluge AW, Kulkarni H, et al. [177Lu-DOTA]0-D-Phe1-Tyr3-Octreotide (177Lu-DOTA TOC) for peptide receptor radiotherapy in patients with advanced neuroendocrine tumours: a phase-II study. *Theranostics*. 2016;6:501-510.
5. Assadi M, Pirayesh E, Rekabpour SJ, et al. 177Lu-PSMA and 177Lu-DOTATATE therapy in a patient with metastatic castration-resistant prostate cancer and neuroendocrine differentiation. *Clin Nucl Med*. 2019;44:978-980.
6. Parghane R V, Naik C, Talole S, et al. Clinical utility of 177 Lu-DOTATATE PRRT in somatostatin receptor-positive metastatic medullary carcinoma of thyroid patients with assessment of efficacy, survival analysis, prognostic variables, and toxicity. *Head Neck*. 2019;44:978-980.
7. Reubi JC, Schär J-C, Waser B, et al. Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. *Eur J Nucl Med Mol Imaging*. 2000;27:273-282.
8. Bodei L, Kidd M, Paganelli G, et al. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. *Eur J Nucl Med Mol Imaging*. 2015;42:5-19.

9. Strosberg J, Wolin E, Chasen B, et al. Health-related quality of life in patients with progressive midgut neuroendocrine tumors treated with 177Lu-Dotatate in the phase III NETTER-1 trial. *J Clin Oncol*. 2018;36:2578-2584.

10. Hammond PJ, Wade AF, Gwilliam ME, et al. Amino acid infusion blocks renal tubular uptake of an indium-labelled somatostatin analogue. *Br J Cancer*. 1993;67:1437-1439.

11. Abbott A, Sakellis CG, Andersen E, et al. Guidance on 177Lu-DOTATATE peptide receptor radionuclide therapy from the experience of a single nuclear medicine division. *J Nucl Med Technol*. 2018;46:237-244.

12. Kwekkeboom DJ, de Herder WW, Kam BL, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0 ,Tyr 3]Octreotate: toxicity, efficacy, and survival. *J Clin Oncol*. 2008;26:2124-2130.

13. Hosono M, Ikebuchi H, Nakamura Y, et al. Manual on the proper use of lutetium-177-labeled somatostatin analogue (Lu-177-DOTA-TATE) injectable in radionuclide therapy (2nd ed.). *Ann Nucl Med*. 2018;32:217-235.

14. Davis AB, Pietryka MH, Passalaqua S. Technical aspects and administration methods of 177 Lu-DOTATATE for nuclear medicine technologists. *J Nucl Med Technol*. 2019;47:288-291.

15. Zaknun JJ, Bodei L, Mueller-Brand J, et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. *Eur J Nucl Med Mol Imaging*. 2013;40:800-816.

16. Cancer Institute N. Common Terminology Criteria for Adverse Events (CTCAE) v5.0.; 2017.

17. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving considerations for PET response criteria in solid tumors. *J Nucl Med*. 2009;50:122S-150S.

18. Brabander T, Van Der Zwan WA, Teunissen JJM, et al. Long-term efficacy, survival, and safety of

[177Lu-DOTA0,Tyr3]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. *Clin Cancer Res*. 2017;23:4617-4624.

19. Hope TA, Abbott A, Colucci K, et al. NANETS/SNMMI procedure standard for somatostatin receptor-based peptide receptor radionuclide therapy with 177Lu-DOTATATE. *J Nucl Med*. 2019;60:937-943.

20. Waser B, Tamma ML, Cescato R, Maecke HR, Reubi JC. Highly efficient in vivo agonist-induced internalization of sst2 receptors in somatostatin target tissues. *J Nucl Med*. 2009;50:936-941.

21. Jacobs S, Schulz S. Intracellular trafficking of somatostatin receptors. *Mol Cell Endocrinol*. 2008;286:58-62.

22. Braat AJAT, Snijders TJ, Seute T, Vonken EPA. Will 177Lu-DOTATATE treatment become more effective in salvage meningioma patients, when boosting somatostatin receptor saturation? A promising case on intra-arterial administration. *Cardiovasc Intervent Radiol*. 2019;42:1649-1652.

DECLARATIONS

Ethics Approval And Consent To Participate

By the retrospective and anonymous nature of the study, the need for approval by an ethics committee was waived.

Consent For Publication

Not applicable.

Availability Of Data And Material

The data that support the findings of this study are available from the corresponding author upon reasonable request**.**

Competing Interests

The authors declare that they have no competing interests.

Funding

No funding was used in performing this study.

Authors' Contributions

ML, BdK and AB were the nuclear medicine physicians in charge of medical care of the treated patients. SE was responsible for all data collection and data analysis. Data analysis was supervised by MB and AB. The laboratory experiment was executed by SE and GK. SE is the main author of this manuscript, all authors reviewed the manuscript and gave consent for publication of the final version.

Acknowledgements

Not applicable.