ORIGINAL ARTICLE

Rapid blood clearance and lack of long-term renal toxicity of Lutetium-177 DOTATATE enables shortening of renoprotective amino acid infusion

Short title: Abbreviated amino acid infusion with LuTate

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DISCLOSURE STATEMENT: The authors have no conflicts of interest to disclose.

Word counts:

Abstract: 262 words | Manuscript: 3022 words

Abstract

Purpose: The aim of the study was to investigate the feasibility of shortening the recommended 4-hour renoprotective amino acid infusion in patients receiving peptide receptor chemo-radionuclide therapy (PRCRT) using radiosensitizing 5-flurouracil (5FU). We evaluated the clearance of radiopeptide from blood, long-term nephrotoxicity in patients undergoing PRCRT with the conventional 4-hour amino acid infusion and renal uptake in patients receiving an abbreviated infusion.

Methods: The whole blood clearance of Lutetium-177 DOTA-octreotate (LuTate) was measured in 13 patients receiving PRCRT. A retrospective analysis of short and long-term change in glomerular filtration rate (GFR) in 96 consecutive patients receiving a 4-hour infusion was performed. Renal LuTate retention was estimated using quantitative SPECT/CT in 22 cycles delivered with a 2.5-hour amino acid infusion and compared to 72 cycles with 4-hour infusion.

Results: LuTate demonstrated bi-exponential blood clearance with an initial clearance half-time of 21 minutes. Approximately 88% of blood activity was cleared within 2 hours. With the 4-hour protocol, there was no significant change in GFR (1.2ml/min mean increase from baseline; 95% CI -6.9 to 4.4ml/min) and no grade 3 or 4 nephrotoxicity at the end of induction PRCRT. The long-term change in GFR after a median follow up of 22 months was 2.2ml/min/year. There was no significant difference in the renal LuTate retention measured in patients receiving a 2.5-hour amino acid infusion compared to those who had a 4-hour infusion.

Conclusions: The greatest renal exposure to circulating radiopeptide occurs in the first 1-2 hours after injection. This, combined with the safety of LuTate PRCRT allows consideration of an abbreviated amino acid infusion, increasing patient convenience and reducing human resource allocation.

Key terms: Lutetium-177 DOTATATE, peptide receptor radionuclide therapy, neuroendocrine tumour, renal toxicity

Introduction

The development of radio-labelled peptides which target somatostatin receptors (SSTR) has been a major advance for both imaging and treatment of neuroendocrine tumours (NETs). Labelling of the peptides with beta particle emitting radionuclides enables specific targeting of the tumours achieving a dose several orders of magnitude higher than healthy tissues, which are therefore relatively spared. Peptide receptor radionuclide therapy (PRRT) is therefore an important treatment option for patients with neuroendocrine tumours (NET). The principal somatostatin analogue currently used in therapy is 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-[Tyr^3]-octreotate (DOTATATE) labelled with indium-111 (InTate), lutetium-177 (LuTate) or yttrium-90 (YTate). PRRT results in improvement of quality of life with high rates of objective tumour responses, reduction of clinical symptoms and prolongation of survival [1-5]. To further improve efficacy, our group has combined the use of PRRT with the radiosensitising agent, 5-fluorouracil (5FU) [6]. The safety profile of such a peptide receptor chemoradionuclide therapy (PRCRT) strategy has been investigated to only a limited extent in the literature [6, 7].

In spite of high and specific tumour uptake with PRRT, physiologic distribution can result in toxicity with the kidneys considered to be the critical, dose-limiting organ. Renal tubular re-absorption of the radio-labelled peptides forms the principal mode of toxicity. This uptake of the radio-peptide is limited to the proximal tubule [8, 9], largely irreversible, and is not observed in cortical glomeruli, distal tubules, medulla, or pelvis [10]. It is also observed in SSTR subtype-2 ($SSTR_2$)-knockout mice, indicating that the mechanism of cortical endocytosis is independent of $SSTR_2$ expression [10]. Therefore the kidneys receive a substantial radiation dose with resultant toxicity ranging from decrease in creatinine clearance [3, 11], proteinuria and hypertension to development of end stage renal disease requiring dialysis [12], and thrombotic microangiopathy [13].

There are several means of minimising the renal radiation effects including altering the structure of the peptide to reduce the renal absorption, infusion of competitive inhibitor agents for peptide uptake pathways, dose fractionation and use of drugs that inhibit renal reabsorption mechanisms or act as radiation protectors [9, 14]. The most widely used strategy is infusing a mixture of the basic amino acids lysine and arginine

prior to and following the radiopeptide to inhibit its absorption competitively [15]. The European Neuroendocrine Tumour Society (ENETS) consensus guidelines recommend intravenous administration of 2.5% lysine, 2.5% arginine in 1 litre of normal saline over 4 hours, starting 30 minutes before the administration of the radiopharmaceutical [16]. Another method is infusion of gelofusine, a gelatin polymer, which inhibits the megalin/cubulin pathway of radiopeptide reabsorption [10].

There has been limited investigation into the optimal time course for amino acid administration. Jamar *et al.* concluded that a 10-hour infusion reduced renal radiation exposure by 10-15% over a conventional 4-hour treatment [17]. Their protocol, however, also involved an increase in the quantity of lysine and arginine delivered from 26.4 to 52.8g. A second study did not identify any difference in kidney dose for different amino acid protocols including 4-5 hours pre-injection, 2 hours pre-injection + 2-3 hours post-injection, 1 hour pre-injection + 2 hours post-injection [18].

Whilst basic amino acid administration is widely regarded as safe practice in order to prevent renal adverse reactions with PRRT, the infusion of a large volume of hypertonic solution is not well tolerated in all patients. Side effects include nausea, vomiting and biochemical effects such as hyperkalaemia [19, 20]. If administered via peripheral veins, we have also observed local thrombo-phlebitic reactions which can result in skin ulceration. A longer length of infusion may also be a practical impediment to efficient delivery of PRRT, particularly when the treatment is given as an outpatient, requiring greater allocation of medical and nursing resources.

The aim of this study is to (1) investigate the pharmacokinetics of LuTate blood clearance with a view to optimisation of reno-protective measures, (2) evaluate the long-term renal toxicity of LuTate PRCRT in a cohort given 4-hour renoprotective amino acid infusion and (3) estimate any difference in renal LuTate retention when using an abbreviated renoprotective infusion.

Materials and Methods:

LuTate blood clearance study

In patients receiving a standard 4-hour amino acid infusion, serial blood samples were collected from 13 of the patients receiving therapeutic dosage of LuTate. Blood samples were collected at times of 0.17, 0.33, 0.5, 1, 2, 4, 24, 48, & 72 hours post-injection. Activity measurements were recorded by well counter (Biodex Medical, Atomlab 950) and decay-corrected with concentration values scaled to percentage of patient maximum recorded at T_0. All components of this study were approved by the Peter MacCallum Ethics Committee. For this prospective component of the study, written informed consent was obtained from all patients.

Long term renal toxicity measurement

Patients

All patients who underwent PRCRT with LuTate and concomitant 5FU between August 2005 and August 2012 at our institute were identified. All these patients had a documented diagnosis of surgically unresectable NET. In addition, adequate SSTR expression for consideration of PRRT was documented with pre-treatment ^{111}In-pentetreotide scintigraphy or ^{68}Ga-DOTATATE PET/CT in all patients by demonstration of intensity of tumoural uptake greater than physiologic liver activity. We excluded patients who had YTate treatment from analysis. A total of 96 patients were identified for analysis. The demographic profile of the patients is represented in the Table 1. All the patients had at least 2 glomerular filtrate rate (GFR) measurements. Sixty-four of the patients had a GFR measurement prior to and at the end of induction regimen.

Treatment protocol:

Lutetium-177 was obtained as $^{177}LuCl_3$ from IDB- Holland (Petten/Baarle Nassau, The Netherlands). ^{177}Lu was labelled to the peptide DOTA-octreotate (provided by the Erasmus Medical Centre, Rotterdam, Netherlands) through chelation to a DOTA molecule forming ^{177}Lu-DOTA-octreotate (LuTate). This labelling procedure is

performed in-house and then used as a therapeutic agent. The labeling efficiency was greater than 95% as determined by thin layer chromatograph (TLC) and high-performance liquid chromatography (HPLC). Each patient received 6-12 GBq LuTate as part of a serial treatment regime: an induction course consisting of 4 cycles separated by 6-8 weeks followed by 1-2 consolidation cycles in selected patients and maintenance of 1 cycle as needed 12-18 months after induction. The dose of LuTate was empirically adjusted according to burden of disease, renal function and body weight. Formal dosimetry was not performed. Excluding the first cycle, radio-sensitising 5FU was administered at a dose of 200mg/m^2/day starting four days prior to radionuclide administration and continuing up to 3 weeks. The maintenance treatment cycles were individualised for each patient depending on the tumour burden, response to treatment and blood counts. Therefore as the time point for maintenance cycles were not uniform in all patients, the time points used for long-term follow-up GFR measurement were at differing intervals and after varying cumulative administered activities. In this cohort of patients receiving a traditional course or renal-protective amino acids, an infusion of 25g lysine and 25g arginine in 1 litre of normal saline was given intravenously over a span of 4 hours commencing at least 30 minutes prior to LuTate administration.

GFR measurement

GFR was measured using ^{51}Cr-EDTA plasma clearance. GFR was also estimated using the Modified Diet in Renal Disease (MDRD) formula (eGFR). The eGFR value was measured prior to initiation of treatment and before every further cycle. ^{51}Cr-EDTA GFR was measured before treatment, prior to last induction cycle and before each maintenance cycle.

Assessment of LuTate renal uptake after abbreviated amino acid infusion

Twenty-two treatment cycles in 14 patients were administered with an abbreviated amino acid regime, consisting of a 2.5-hour infusion beginning 30 minutes prior to LuTate therapy. Lysine and arginine were administered at the same rate and concentration, yielding a total dose of reno-protective amino acids of 625-750 mL (16-19g of lysine and arginine). Patients with impaired renal function (GFR < 60ml/min) or a small tumour burden were ineligible for an abbreviated amino acid

infusion protocol. The comparison group was 72 consecutive treatment cycles in 45 patients receiving the standard 4-hour infusion.

Renal LuTate retention was measured with SPECT/CT (Siemens Symbia T6, Munich, Germany) using a quantitative SPECT (Q-SPECT) protocol described previously (25). Images were acquired at 24 hours post-injection of LuTate. Kidney volumes were segmented based on anatomical delineation on CT image sets. The resulting volume of interest was used to record the mean renal standardized uptake value (SUV) on the Q-SPECT dataset.

Statistical analysis

A paired t-test was conducted to compare GFR at baseline and at post induction for each of the subgroups. In order to overcome the difference in the GFR time points and account for all the serial values of GFR measurement, a longitudinal linear regression model with patient and time as the random effects was used to estimate the rate of change in GFR over time. The slope of the curve was obtained to estimate the rate of change of GFR per year. Multivariate analysis was done using ANCOVA test to determine factors associated with the long term change of GFR. Factors considered were: age, grade of renal uptake of radionuclide, cumulative dose, mean dose per cycle, diabetes, hypertension and history of previous chemotherapy. Correlation between GFR and eGFR values at baseline and on last follow up were evaluated using Spearman's rank correlation coefficient. A two-sided p value of <0.05 was considered significant. For analysis of the abbreviated amino acid infusion, the difference in mean 24-hour renal SUV between abbreviated and 4-hour amino acid cohorts was compared by unpaired t-test.

Results:

LuTate blood clearance study

Serial blood samples indicate that LuTate clearance obeys a bi-exponential clearance model from the bloodstream (Figure 1). Very rapid clearance is observed in the first 1-2 hours of treatment. The initial clearance half-time is measured at 20.8 minutes. After 4 hours, clearance slows with measurements indicating a long-term biological half-life of 12.9 hours. Results show that after the first 2-hours of administration,

blood-pool radioisotope concentration is reduced to 12.1% of its level immediately after injection. At times of 24, 48, and 72 hours, intravenous LuTate concentration is further reduced to 1.8, 0.9, and 0.8% of the initial value. Long-term blood-pool LuTate retention is attributed to a near equilibrium of renal excretion and washout from tumour volume and other organs.

Long-term renal toxicity

In patients who had ^{51}Cr EDTA GFR measured prior to and at the end of induction therapy (n=64), the change in the mean GFR after a mean administered activity of 24.6 GBq over 2.8 cycles was 1.2 ml/min (95% CI -6.9 to 4.4ml/min) and this was not statistically significant. A sub-group analysis based on grade of baseline GFR is shown in Table 2. Interestingly, patients with impaired renal function at baseline showed a trend to improving renal function although this was not statistically significant.

In long term follow-up, the mean rate of decline of GFR that was estimated in patients who had more than 2 GFR measurements (n=44) was 2.2ml/min/year (95% CI: 4.1 to 0.3 ml/min/year) (Figure 2). We also evaluated the correlation of the eGFR estimated by MDRD formula with the GFR estimated by ^{51}Cr-EDTA method. There was good correlation between the two values (Spearman's rho = 0.57 $p<0.05$) suggesting that this measure can be used as a reasonable surrogate for renal function when ^{51}Cr-EDTA is not available. Multivariate analysis for long term change in GFR showed that prior chemotherapy was the only factor which had statistically significant association ($p<0.05$).

Assessment of LuTate renal uptake after abbreviated amino acid infusion

In the patients receiving an abbreviated infusion protocol a small but not significant increase in renal retention of LuTate (5.8%, p=0.26) was observed on Q-SPECT imaging at 24 hours compared with the patients receiving the standard 4-hour infusion protocol. Biological factors that may impact on SUV computation or renal retention including administered LuTate dosage, patient weight, and functional renal volume were comparable between the two groups (see Table 3).

Discussion:

Renal toxicity is a concern with PRRT as the principal mode of excretion of somatostatin analogues is through the kidneys and this is associated with uptake and retention of a proportion of the filtered peptide in the proximal convoluted tubules. This is particularly the case with ^{90}Y-bassed PRRT, presumably due to the long beta path length of ^{90}Y that allows beta particles to reach the glomeruli-rich cortical region of the kidney. Otte *et al.* [11] described stable renal insufficiency in 2 patients and renal failure requiring dialysis in a further 2 of 29 patients receiving ^{90}Y-DOTATOC. All the patients with renal side effects did not have a reno-protective infusion. They also reported another case of end stage renal disease developing after PRRT with ^{90}Y-DOTATOC despite renal protection with Hartmann HEPA 8% solution [11]. In a large series of 1109 patients [2] receiving 2472 cycles of ^{90}Y-DOTATOC receiving renoprotective arginine and lysine infusion, 102 patients (9.2%) experienced severe permanent renal toxicity (grade 4, 67 patients; grade 5, 35). Toxicity was more common in patients with advanced age, low baseline GFR and high renal uptake of tracer. In contrast to these results, Kwekkeboom *et al.* documented that renal toxicity occurred in only 2 of 504 patients treated with LuTate with reno-protective infusion [4]. A preliminary report by van Essen *et al.* [12] showed no renal toxicity in 7 patients treated with concomitant oral capecitabine and LuTate during short-term follow-up. A preliminary analysis published from our centre also showed no acute or long-term changes in a smaller group of 27 patients treated with LuTate with infusional 5FU and also receiving a 4-hour amino acid infusion [6, 7].

Although amino acid infusions appear to be beneficial in reducing nephrotoxicity, it is not without side-effects. Giovacchini *et al.* [21] demonstrated that transient hyperkalemia frequently occurs with administration of amino acid infusions. Rolleman *et al.* reported that although the kidney radiation dose was lower in patients receiving an infusion containing 75g lysine, these patients also exhibited a much higher incidence of hyperkalemia, vomiting in up to 50% of patients and muscle weakness in one patient [20]. These side effects were attributed to both the quantity of amino acid and the hypertonicity of the solution that was administered. Barone *et al.* [19] also described hypophosphatemia. The elevation of potassium levels has been proven to be highest with infusion of 75g lysine alone. We have also noted local

cutaneous and phlebitic reactions late during infusion of amino acids into a peripheral vein. Furthermore, a 4-hour infusion limits the potential feasibility of administering PRCRT as an outpatient in jurisdictions where this is allowable. It also requires significant allocation of staff to supervise treatment, increasing its cost. Therefore, if reduction in the duration of this infusion were safe, it would have significant clinical advantages.

In this study we analysed the renal toxicity profiles in 96 patients undergoing PRCRT with concomitant 5FU as radiosensitiser. We measured GFR with ^{51}C-EDTA plasma clearance as this is a more accurate parameter than serum creatinine or eGFR [22]. We demonstrate no significant change in the mean GFR at the end of induction therapy in 65 patients. Whilst mild renal toxicity (grade 1 and 2) was noted in 8 patients, there were no patients who developed grade 3 or 4 renal toxicity. Interestingly, patients with baseline impairment of renal function did not have a more marked fall in GFR (Table 2). Rather, there was actually a trend towards improvement in renal function over time. Although not statistically significant and warranting further evaluation, it is postulated that impaired glomerular filtration may decrease presentation of radiopeptide to the proximal tubules, increasing circulation time and increasing bioavailability for tumour uptake. This could augment therapeutic index and, given that many patients with advanced NET have extensive liver involvement, response in liver disease may reduce hepato-renal syndrome.

We also analysed long term renal effects of PRCRT with a median follow up period of 22 months in the entire cohort of 96 patients. The mean rate of decline in GFR was 2.2 ml/min per year. This change in GFR appears only marginally more than the average age-related drop in creatinine clearance of 0.75ml/min/year showed by Lindeman *et al.* [23] and is of minor clinical significance. Our results are consistent with the results of Bodei *et al.* [24] who showed that after a median follow up period of 30 months, none of the patients treated with LuTate PRRT without chemotherapy showed renal toxicity. This further suggests that addition of radiosensitising chemotherapy does not increase the renal toxicity compared to standalone PRRT. Therefore, there seems to be an acceptable therapeutic index with this therapy to consider a less aggressive renoprotective amino acid infusion protocol.

Imaging and blood sample measurements indicate that the pharmacokinetics of somatostatin-analogues in radionuclide therapy obey two phases. Initial organ uptake mostly occurs in the first one to two hours after injection of therapeutic agent. This phase is marked by rapid clearance from the bloodstream with a clearance half-time of approximately 20 minutes. Clearance is primarily attributed to absorption by tumour, liver, and spleen with simultaneous renal excretion. Following tissue uptake, washout occurs at a much slower rate. Therefore the initial 2-3 hours of the uptake phase, representing approximately 6-9 of the rapid clearance half-times, is the ideal time for the reno-protective amino acid infusion. These results are consistent with measurements made by Jamar *et al.* [17]. We have previously shown an inverse relation between both tumour burden and patients' size and renal retention of radiopeptide [25]. Accordingly, patients with a small disease volume or small body habitus may still warrant a longer infusion time and this should also be considered in patients with pre-existing renal impairment.

Given the rapid clearance of LuTate from blood, we proposed that a shorter duration of amino acid infusion would provide equivalent renoprotection. We demonstrated that patients who received the shorter infusion had no significant increase in renal concentration of LuTate compared to patients receiving the conventional 4-hour reno-protective amino acids infusions (Table 3). The major limitation of this analysis is the lack of formal dosimetric data for the kidneys. Both prospective and retrospective dosimetry calculations have their own limitations. With respect to prospective dosimetry, the lack of amino acid infusion at the time of pre-therapy diagnostic somatostatin analogue imaging (In-111 octreotide or Ga-68 octreotate) significantly limits the ability to assess likely renal dose. Therefore we have adopted a pragmatic dosing regimen that assigned an administered activity ranging from 6-12 GBq based on a combination of tumour burden primarily but also influenced by renal function and body habitus as well as pre-existing myelosuppresion, e.g. from previous chemotherapy. Other aspects considered in determining the dose also included logistic aspects such as the dose delivered by the supplier and the number of patients being treated on the given day. However, the quantitative SUV data from the SPECT/CT imaging has been used a surrogate for renal dose [26]. We are continuing follow-up of patients receiving the abbreviated amino acid infusions to confirm that long-term renal function is not compromised.

Conclusion:

Serial blood data indicate that the greatest renal exposure to circulating radiopeptide occurs in the first 1-2 hours after injection. Since peptide receptor chemo-radionuclide therapy with LuTate and concomitant 5FU when combined with a renoprotective amino acid infusion has minimal acute or long-term renal toxicity, we therefore propose that it would be safe on the basis of these data to shorten the duration of amino acid infusion to 30 minutes prior and 2 hours after LuTate infusion in selected patients. This would make the treatment more convenient for patients and more practical for medical staff while simultaneously limiting potential direct side effects.

Acknowledgement:

Professor Hicks and Dr Jackson were supported by a Translational Research Grant from the Victorian Cancer Agency. Dr K Raghava Kashyap was supported by Endeavour Awards, a venture of Austraining International in partnership with Department of Education, Employment and Workplace Relations, Government of Australia. We would like to acknowledge the support and inspiration provided to our facility over the past 15 years from the Department of Nuclear Medicine at the Erasmus Medical Centre under the leadership of Professor Eric Krenning.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

References:

1. Bodei L, Cremonesi M, Grana CM, Fazio N, Iodice S, Baio SM, et al. Peptide receptor radionuclide therapy with (1)(7)(7)Lu-DOTATATE: the IEO phase I-II study. Eur J Nucl Med Mol Imaging. 2011;38:2125-35. doi:10.1007/s00259-011-1902-1.
2. Imhof A, Brunner P, Marincek N, Briel M, Schindler C, Rasch H, et al. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. J Clin Oncol. 2011;29:2416-23. doi:10.1200/JCO.2010.33.7873.
3. Kwekkeboom DJ, Bakker WH, Kam BL, Teunissen JJ, Kooij PP, de Herder WW, et al. Treatment of patients with gastro-entero-pancreatic (GEP) tumours with the novel radiolabelled somatostatin analogue [177Lu-DOTA(0),Tyr3]octreotate. Eur J Nucl Med Mol Imaging. 2003;30:417-22. doi:10.1007/s00259-002-1050-8.
4. Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol. 2008;26:2124-30. doi:10.1200/JCO.2007.15.2553.
5. Kwekkeboom DJ, Teunissen JJ, Bakker WH, Kooij PP, de Herder WW, Feelders RA, et al. Radiolabeled somatostatin analog [177Lu-DOTA0,Tyr3]octreotate in patients with endocrine gastroenteropancreatic tumors. J Clin Oncol. 2005;23:2754-62. doi:10.1200/JCO.2005.08.066.
6. Hubble D, Kong G, Michael M, Johnson V, Ramdave S, Hicks RJ. 177Lu-octreotate, alone or with radiosensitising chemotherapy, is safe in neuroendocrine tumour patients previously treated with high-activity 111In-octreotide. Eur J Nucl Med Mol Imaging. 2010;37:1869-75. doi:10.1007/s00259-010-1483-4.
7. Claringbold PG, Brayshaw PA, Price RA, Turner JH. Phase II study of radiopeptide 177Lu-octreotate and capecitabine therapy of progressive disseminated neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2011;38:302-11. doi:10.1007/s00259-010-1631-x.
8. Lambert B, Cybulla M, Weiner SM, Van De Wiele C, Ham H, Dierckx RA, et al. Renal toxicity after radionuclide therapy. Radiat Res. 2004;161:607-11.
9. Vegt E, de Jong M, Wetzels JF, Masereeuw R, Melis M, Oyen WJ, et al. Renal toxicity of radiolabeled peptides and antibody fragments: mechanisms, impact on radionuclide therapy, and strategies for prevention. J Nucl Med. 2010;51:1049-58. doi:10.2967/jnumed.110.075101.
10. Melis M, Krenning EP, Bernard BF, Barone R, Visser TJ, de Jong M. Localisation and mechanism of renal retention of radiolabelled somatostatin analogues. Eur J Nucl Med Mol Imaging. 2005;32:1136-43. doi:10.1007/s00259-005-1793-0.
11. Otte A, Herrmann R, Heppeler A, Behe M, Jermann E, Powell P, et al. Yttrium-90 DOTATOC: first clinical results. Eur J Nucl Med. 1999;26:1439-47.
12. van Essen M, Krenning EP, Kam BL, de Herder WW, van Aken MO, Kwekkeboom DJ. Report on short-term side effects of treatments with 177Lu-octreotate in combination with capecitabine in seven patients with gastroenteropancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2008;35:743-8. doi:10.1007/s00259-007-0688-7.

13. Cybulla M, Weiner SM, Otte A. End-stage renal disease after treatment with 90Y-DOTATOC. Eur J Nucl Med. 2001;28:1552-4. doi:10.1007/s002590100599.
14. Rolleman EJ, Melis M, Valkema R, Boerman OC, Krenning EP, de Jong M. Kidney protection during peptide receptor radionuclide therapy with somatostatin analogues. Eur J Nucl Med Mol Imaging. 2010;37:1018-31. doi:10.1007/s00259-009-1282-y.
15. Hammond PJ, Wade AF, Gwilliam ME, Peters AM, Myers MJ, Gilbey SG, et al. Amino acid infusion blocks renal tubular uptake of an indium-labelled somatostatin analogue. Br J Cancer. 1993;67:1437-9.
16. Kwekkeboom DJ, Krenning EP, Lebtahi R, Komminoth P, Kos-Kudla B, de Herder WW, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: peptide receptor radionuclide therapy with radiolabeled somatostatin analogs. Neuroendocrinology. 2009;90:220-6. doi:10.1159/000225951.
17. Jamar F, Barone R, Mathieu I, Walrand S, Labar D, Carlier P, et al. 86Y-DOTA0)-D-Phe1-Tyr3-octreotide (SMT487)--a phase 1 clinical study: pharmacokinetics, biodistribution and renal protective effect of different regimens of amino acid co-infusion. Eur J Nucl Med Mol Imaging. 2003;30:510-8. doi:10.1007/s00259-003-1117-1.
18. Bodei L, Cremonesi M, Zoboli S, Grana C, Bartolomei M, Rocca P, et al. Receptor-mediated radionuclide therapy with 90Y-DOTATOC in association with amino acid infusion: a phase I study. Eur J Nucl Med Mol Imaging. 2003;30:207-16. doi:10.1007/s00259-002-1023-y.
19. Barone R, Pauwels S, De Camps J, Krenning EP, Kvols LK, Smith MC, et al. Metabolic effects of amino acid solutions infused for renal protection during therapy with radiolabelled somatostatin analogues. Nephrol Dial Transplant. 2004;19:2275-81. doi:10.1093/ndt/gfh362.
20. Rolleman EJ, Valkema R, de Jong M, Kooij PP, Krenning EP. Safe and effective inhibition of renal uptake of radiolabelled octreotide by a combination of lysine and arginine. Eur J Nucl Med Mol Imaging. 2003;30:9-15. doi:10.1007/s00259-002-0982-3.
21. Giovacchini G, Nicolas G, Freidank H, Mindt TL, Forrer F. Effect of amino acid infusion on potassium serum levels in neuroendocrine tumour patients treated with targeted radiopeptide therapy. Eur J Nucl Med Mol Imaging. 2011;38:1675-82. doi:10.1007/s00259-011-1826-9.
22. Hartlev LB, Boeje CR, Bluhme H, Palshof T, Rehling M. Monitoring renal function during chemotherapy. Eur J Nucl Med Mol Imaging. 2012;39:1478-82. doi:10.1007/s00259-012-2158-0.
23. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. J Am Geriatr Soc. 1985;33:278-85.
24. Bodei L, Cremonesi M, Ferrari M, Pacifici M, Grana CM, Bartolomei M, et al. Long-term evaluation of renal toxicity after peptide receptor radionuclide therapy with 90Y-DOTATOC and 177Lu-DOTATATE: the role of associated risk factors. Eur J Nucl Med Mol Imaging. 2008;35:1847-56. doi:10.1007/s00259-008-0778-1.
25. Beauregard JM, Hofman MS, Kong G, Hicks RJ. The tumour sink effect on the biodistribution of 68Ga-DOTA-octreotate: implications for peptide receptor radionuclide therapy. Eur J Nucl Med Mol Imaging. 2012;39:50-6. doi:10.1007/s00259-011-1937-3.
26. Beauregard JM, Hofman MS, Pereira JM, Eu P, Hicks RJ. Quantitative (177)Lu SPECT (QSPECT) imaging using a commercially available SPECT/CT system. Cancer Imaging. 2011;11:56-66. doi:10.1102/1470-7330.2011.0012.

Table 1: GFR Analysis: baseline patient characteristics (N=96)

Characteristic	
Age (years)	
Mean (SD)	59 (12)
Median (range)	62 (23-79)
Gender, n (%)	
Female	40 (42%)
Male	56 (58%)
Diagnosis	
Pancreatic NET	30 (32%)
Metastatic NET of unknown primary	24 (25%)
Mid-gut Carcinoid	29 (30%)
Gastrinoma	4 (4%)
Insulinoma	4 (4%)
Glucagonoma	2 (2%)
Pheochromocytoma	2 (2%)
Vipoma	1 (1%)
Comorbidities, n (%)	
Diabetes	21 (22%)
Hypertension	22 (23%)
Prior chemotherapy, n (%)	
Yes	26 (27%)

Table 2. Difference in baseline and post induction GFR in patients categorized into groups of normal, mild and moderate baseline renal dysfunction.

		GFR : Mean (StdDev)			Paired t-test
		Baseline	Post	Difference:	p-value
Baseline GFR	n		Induction	Mean (StdDev)	
>90 ml/min	34	123.3 (27.7)	120.0(33.2)	-3.2 (21.8)	0.39
60-90 ml/min	24	79.9 (7.5)	84.0 (22.6)	4.0 (22.3)	0.38
30-60 ml/min	6	51.8 (7.1)	70.2 (26.7)	18.3 (25.1)	0.13

Table 3. Renal Standardised Uptake Values (SUVs) for patients receiving conventional (4-hour) and abbreviated (2.5-hour) amino acid regimes in conjunction with LuTate PRCRT. Increased renal LuTate retention is observed in patients receiving an abbreviated amino acid infusion, although the difference is not significant.

Group	2.5-Hour AA	4-Hour AA
Follow-up SPECT Studies	22	72
Average ^{177}Lu-Octreotate Activity (MBq)	7064	7273
Patients	14	45
Average weight (kg)	78	78
Percentage Male/Female	46/54%	49/51%
Average Segmented Kidney Volume (cc)	374	370
Mean Renal SUV (24 hours PI)*	4.17 ± 1.22 *(*p*=0.259)	3.94 ± 1.39

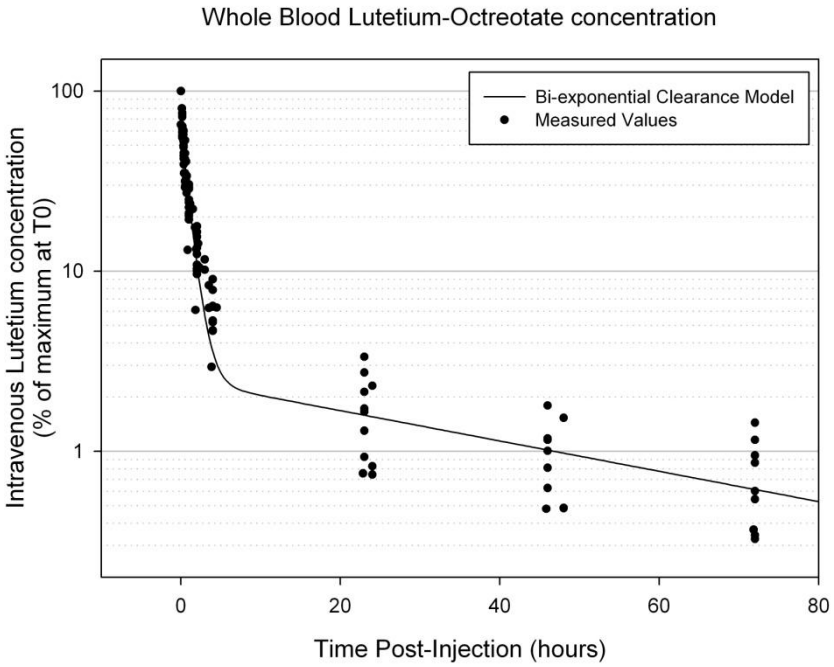

Figure 1: Intravenous LuTate concentrations obtained through serial blood sampling during radionuclide therapy of thirteen patients. Rapid clearance is observed in the first 2 hours following administration, a finding attributed to rapid but saturable organ and tumour uptake and redistribution in the extra-cellular space. Solid line indicates bi-phasic, double-exponential fit of clearance model. Initial clearance half-time is 21 minutes.

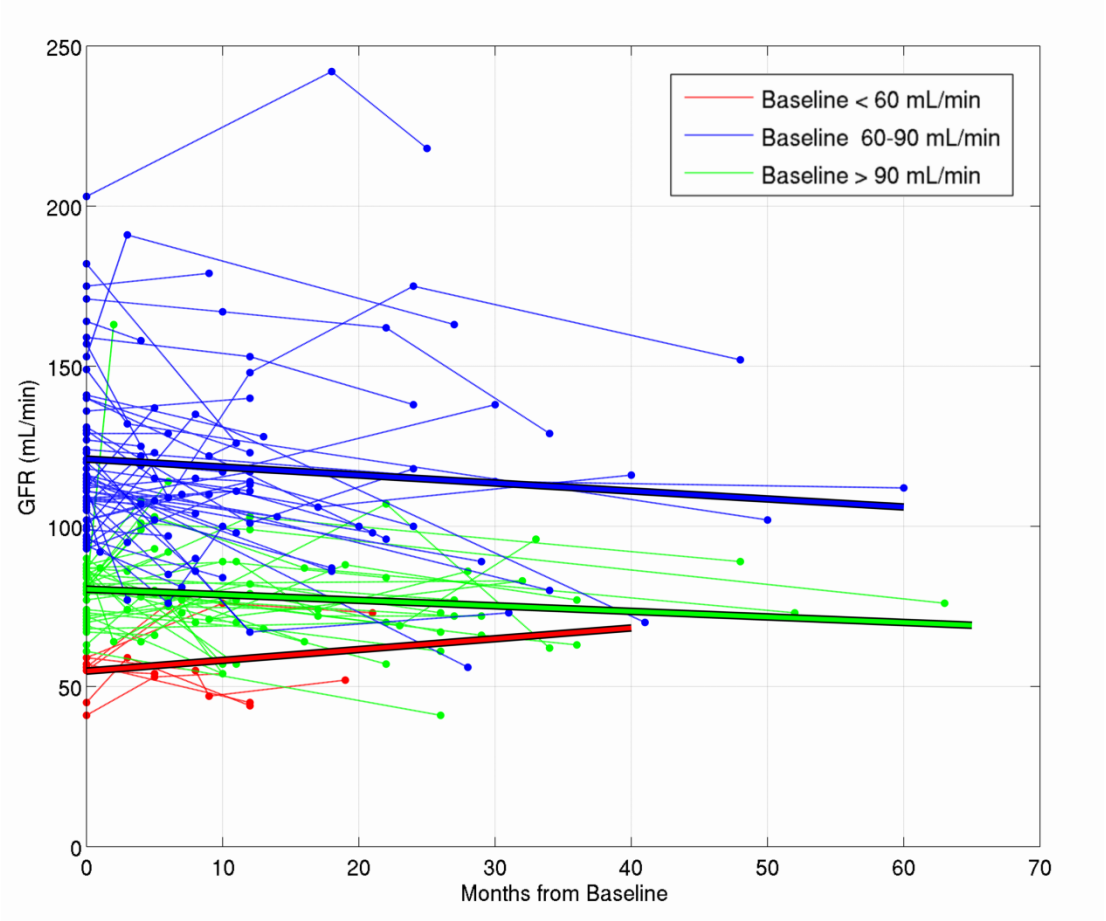

Figure 2: GFR measures over time with regression slopes stratified by degree of baseline renal impairment.