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^{177}Lu-DOTATATE based PRRT in patients of Metastatic Neuroendocrine tumor with single functioning kidney: Evaluation of tolerability and effect on Renal Function Parameters

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Short Running Title: PRRT in single functioning kidney

^{177}Lu-DOTATATE based PRRT in patients of Metastatic Neuroendocrine tumor with single functioning kidney: Evaluation of tolerability and effect on Renal Function Parameters

Abstract:

Aims and Objectives: Assessment of renal toxicity profile of 177Lu-DOTATATE based Peptide Receptor Radionuclide therapy (PRRT) in patients of Metastatic Neuroendocrine tumor (NET) with a single functioning kidney.

Materials and Methods: This was a retrospective analysis of NET patients, who had undergone PRRT with ^{177}Lu-DOTATATE at a large tertiary care centre. The patients selected for the study fulfilled the following criteria: (i) all patients were cases of somatostastin receptor (SSTR) positive neuroendocrine tumours who had received at least 3 cycles of PRRT with 177Lu-DOTATATE and (ii) had a documented single functioning kidney. The selected patients were analyzed under the following parameters: (i) the patient characteristics, (ii) associated metastatic burden, (iii) renal parameters at diagnosis and during the course of therapy, (iv) evaluation of associated nephrotoxic factors. For renal assessment, following parameters were studied before each PRRT cycle: (i) glomerular filtration rate (GFR) estimated by 99mTc-DTPA renogram study, (ii) Effective Renal Plasma Flow (ERPF) by 99mTc-EC renogram study, (iii) blood urea and serum creatinine levels. Renal toxicity was evaluated using Common Terminology Criteria for Adverse Events v4.0 (NCI-CTCAE score). The percentage reduction in the GFR and ERPF for all patients was also assessed. Calculation of filtration fraction (FF) was undertaken to clarify whether there has been a relatively greater reduction in one of the two indices of renal function compared to the other.

Results: At the time of analysis, six patients with single functioning kidney with metastatic NET received PRRT with ^{177}Lu-DOTATATE between 3-5 cycles and cumulative activity of 16.6 GBq to 36.2 GBq. Duration of follow-up ranged from 12 - 56 months. Overall toxicity profile (as per the NCI-CTCAE score) showed no patients had any acute renal toxicity. Three patients had no overall chronic renal toxicity; one patient had grade II chronic renal toxicity and two patients had grade I chronic renal toxicity level **.** All the patients who showed overall chronic renal toxicity showed compromised renal function at the onset (baseline chronic renal toxicity). Interestingly, the two patients with resultant grade I chronic renal toxicity level post-PRRT had grade II chronic renal toxicity before commencement of PRRT with gradual improvement over the subsequent cycles. One patient had grade II chronic renal toxicity before commencement of PRRT with transient worsening to grade III toxicity after first cycle PRRT with gradual improvement and return to basal levels post second cycle of PRRT (values revert back to the grade II toxicity grade). Only two patients showed reduction in GFR (one patient had 5.3% reduction whereas one patient had 13.84% reduction). Four patients showed a reduction in the ERPF (with one patient showing maximum reduction in ERPF it being 31.39% from basal ERPF) and all the four demonstrated rise in filtration fraction signifying that tubular parameters are more affected compared to the glomerular parameters.

Conclusion: The preliminary results of this analysis show the feasibility of 177-Lu DOTATATE based PRRT in patients of NET with single functioning kidney, along with proper renal protection and dose fractionation. Further studies are required to assess the long term renal consequences of the changes in ERPF and FF parameters in these patients.

Introduction:

Peptide receptor radionuclide therapy (PRRT) with ^{177}Lutetium or 90-Yttrium labelled somatostatin receptor analogues has been widely used for targeted treatment of metastatic/inoperable neuroendocrine tumours (NET). In addition to bone marrow, the absorbed dose to the kidney is a well-perceived limiting factor for PRRT, with reported documentation of dose related renal toxicity in the literature (*1-3*). Patients with a single functioning kidney form a distinct clinical subset who obviously can have clinical concerns with respect to the tolerability compared to those with both functioning kidneys; hence, it is imperative to observe and accrue the renal profile data in this particular subset following PRRT, so as to assess the risk and feasibility of this therapy in this group of patients.

Hence, the premise of this retrospective analysis was to evaluate the renal profile (focusing primarily on renal toxicity) of this particular subset of patients selected from those who had undergone PRRT over the last 5 years in a large tertiary care centre. For an appropriate assessment of toxicity profile, patients who had received at least 3 cycles of PRRT were selected. In our analysis, however, there was no patient of this particular subgroup who received lesser than 3 cycles or whom PRRT was terminated with fewer cycles at the time of the study.

Materials and Methods:

This is a retrospective analysis of NET patients, who had undergone PRRT with 177Lu-DOTATATE at a large tertiary care centre and was selected from a population of 295 patients treated over last 5 years. The patients selected for the study fulfilled the following criterion: all patients were cases of SSTR positive neuroendocrine tumours,

demonstrated a single functioning kidney and had received at least 3 cycles of PRRT with 177Lu-DOTATATE (Dose of each cycle ranged 5.5 GBq-7.4 GBq, based upon whether given in metastatic or in the neoadjuvant setting, though in this case all patients received 5.5. GBq as they had metastatic disease). All the patients were subjected to the single day amino acid renal protection protocol (designed to deliver the recommended 25 g lysine and 25 g arginine infused over 7.5 to 8 hours, the amino acid infusion starting 60 minutes before therapy). No specific adjustment as such was applied for the single functioning kidney.

The selected patients were analyzed under the following parameters: (i) the patient characteristics, (ii) associated metastatic burden, (iii) renal parameters at diagnosis and during the course of therapy, (iv) evaluation of associated nephrotoxic factors. All patients underwent glomerular filtration rate (GFR) estimation by gamma camera based 99mTc-DTPA renogram study and Effective Renal Plasma Flow (ERPF) by 99mTc-EC renogram study before each cycle of PRRT. Additionally, to clarify and expand the point of differential affection, calculation of filtration fraction was undertaken using the formula FF= (GFR/ERPF). Presentation of GFR and ERPF data in terms of filtration fractions is useful when both parameters of renal function decrease (as frequently occurs in renal insufficiency) and can clarify if there has been a relatively greater reduction in one of the two indices of renal function compared to the other (e.g., a relatively greater reduction in ERPF compared to GFR would lead to an increase in filtration fraction while the opposite would occur if there were a relatively greater reduction in GFR compared to ERPF).

Also evaluation of blood urea levels and serum creatinine was also undertaken at each time point of assessment. History regarding risk factors known to be associated with renal toxicity was assessed. During each PRRT cycle, the standard protocol was followed as suggested by the guidelines for PRRT (*3*).

Renal toxicity was evaluated using Common Terminology Criteria for Adverse Events v4.0 (NCI-CTCAE score) (*4*). They are summarized as follows: [a] the Criteria for Chronic Renal toxicity [as per CTCAE 4]:- Grade I (+): eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN -60 mL/min/1.73 m^2 or proteinuria 2+ present; urine protein/creatinine >0.5; Grade II (++): eGFR or CrCl 59 – 30 mL/min/1.73 m^2 ; Grade III (+++) : eGFR or CrCl 29 – 15 mL/min/1.73 $m^{2,}$ Grade IV (++++) : eGFR or CrCl <15 mL/min/1.73 m^2; dialysis or renal transplant indicated; Grade V (+++++) : Death.

[b] The Criteria for Acute Renal toxicity [as per CTCAE 4] (*4*): Grade I (+) :- Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 times above baseline; Grade II (++) : Creatinine 2 - 3 times above baseline; Grade III (+++) : Creatinine more than 3 times above baseline or >4.0 mg/dL; hospitalization indicated; Grade IV (++++) : Life-threatening consequences; dialysis indicated; Grade V (+++++) : Death.

Results:

Among the entire population of 295 patients that were analyzed 6 patients were found to have a single functioning kidney. Out of the 6 patients 3 patients were female and 3 patients were male. The age group of these patients ranged from 33-63 years (**Table 1**). Of these 6 patients 2 patients had pancreatic NET, 1 patient had NET of kidney, 1 patient had NET of ureter, 1 patient had NET of small bowel whereas one patient had metastatic NET of unknown primary. Associated sites of metastasis in addition to that of primary were liver (most common; seen in 4 patients), skeletal sites (in 2 patients) and adrenal gland (in 1 patient). Histopathologically, 2 patients each were of well differentiated NET, intermediate grade NET and poorly differentiated NET **(Table 1).** In the selected group 5 patients had a functioning right kidney whereas 1 patient had a functioning left kidney. The causes for single functioning kidney included extension of the tumour into the kidney, genitourinary tract NET (ureter NET

and horse shoe kidney NET), congenital anomalies of the kidney and idiopathic incidental detection of single functioning status (**Table 2**). 5 of the 6 patients had grade IV uptake (uptake more than liver uptake) on SSTR imaging with a single patient showing grade III uptake (uptake equal to liver uptake) **(Table 3)**. All the patients had severe systemic complaints due to the functioning nature of the underlying NET which were not relieved by oral medication as well as by somatostatin analogues. Hence these patients were subjected to PRRT **(Table 3)**.

Associated risk factors known to have nephrotoxicity were also assessed. These were long standing hypertension (duration of more than 10 years), diabetes mellitus (duration of more than 10 years) and any known prior nephrotoxic chemotherapy administration. One patient had past history of hypertension, one patient had past history of diabetes mellitus; two patients had prior history of chemotherapy with 6 cycles of cisplatin whereas a single patient had previous chemotherapy with capecitabine **(Table 4).**

At the time of analysis, the patients received PRRT with ^{177}Lu-DOTATATE between 3-5 cycles and cumulative activity of 16.6 GBq to 36.2 GBq **(Table 4)**. Duration of follow-up ranged from 12 to 56 months. As per the NCI-CTCAE score (*4*), overall toxicity profile showed no patients had any acute renal toxicity but one patient had grade II chronic renal toxicity (Case III) and two patients had grade I chronic renal toxicity (Case IV and VI) **(Table 5).** All the patients who demonstrated overall chronic renal toxicity, also showed compromised renal function at the onset (baseline chronic renal toxicity). Three patients showed no overall chronic renal toxicity.

Also analysis was done after each individual cycle **(Table 6)** with the use of the NCI-CTCAE score. No patients showed evidence of any acute renal toxicity overall as well as after each individual cycle. 2 patients showed transient grade I chronic renal toxicity after the first cycle of PRRT with improvement and normalization in subsequent cycles. 2 patients had grade II chronic renal toxicity before commencement of PRRT with gradual improvement over the subsequent cycles with resultant grade I

chronic renal toxicity post PRRT. 1 patient had grade II chronic renal toxicity before commencement of PRRT with transient worsening to grade III toxicity after first cycle PRRT with gradual improvement and return to basal levels post second cycle of PRRT (values revert back to the grade II toxicity grade) **(Table 6).** One patient had no chronic renal toxicity overall as well as after each individual cycle.

Overall percentage reduction in the GFR and ERPF for all patients was also assessed. It was seen that only 2 patients showed reduction in GFR (1 patient had 5.3% reduction whereas one patient had 13.9% reduction). 4 patients showed a reduction in the ERPF (case II showed maximum reduction in ERPF it being 31.4% from basal ERPF) **(Table 7).** All the 4 patients demonstrated rise in filtration fraction signifying that tubular parameters are more affected compared to the glomerular parameters **(Table 7 and Fig 1, Table 8)**. The biochemical tumor markers (Serum Chromogranin A) evaluated has been summarized in **Table 2**.

Discussion:

PRRT is increasingly popular therapeutic modality which is being widely used in the management of advanced neuroendocrine tumours (*5*). The recent guidelines state that PRRT can be used in patients with metastatic neuroendocrine tumour of well differentiated and intermediate grade tumours (Ki67 index < 20%). The ESMO guidelines suggest that the PRRT can be given upto NET with Ki67 index <30% (*6*).

No overall acute renal toxicity was observed in any of the patients with a single patient showing Grade II chronic renal toxicity and 2 patients showed grade I renal toxicity post-PRRT. The patient who showed grade II renal toxicity (post 5 cycles PRRT), had compromised renal function (grade II chronic renal toxicity) even before PRRT as well. Two patients who showed overall Grade I chronic renal toxicity had grade II chronic renal toxicity at the onset before undertaking the PRRT. Three patients showed no chronic renal toxicity. An observation worth to note was that in 3 patients (2

among them with no resultant renal toxicity and 1 with grade II renal toxicity) there was some transient deterioration of renal function post first cycle of PRRT with improvement over subsequent cycles.

Assessment of associated nephrotoxic factors (long standing hypertension, diabetes, nephrotoxic chemotherapy) is essential in evaluation of subsequent renal dysfunction post PRRT. Renal dysfunction may be aggravated in patients in whom these factors coexist (*7*). In our analysis, one patient who had previous cisplatin based chemotherapy had grade II chronic renal toxicity following PRRT, but this patient had compromised renal function even at baseline. The other patient who received cisplatin based chemotherapy had a transient chronic renal toxicity post first cycle which reversed over to normal values over a period of time following the second cycle. The same patient had long standing diabetes. One patient having long standing hypertension had a transient chronic renal toxicity post first cycle which also reversed to normal values over a period of time after the second cycle. Thus it was seen that even with a single functioning kidney and presence of other nephrotoxic features and factors, there was no obvious evidence of significant renal toxicity associated with ^{177}Lu DOTATATE based PRRT.

To reduce the tubular reabsorption, positively charged amino acids, such as L-lysine and/or L-arginine, are coinfused to competitively inhibit the proximal tubular reabsorption of the ^{177}Lu based DOTA analogues. The coadministration of these amino acids leads to a significant reduction in the renal absorbed dose, which ranges from 9% to 53% (*8*). Dose fractionation is also propagated in such high risk cases in whom renal toxicity is more likely than in normal patients. In all our cases adequate renal protection with coinfusion of amino acids and dose fractionation was followed. As no renal toxicity was seen in any of the patients the importance of the above mentioned practices is seen.

More number of patients in our group showed some decline in the ERPF (4 out of 6) than GFR (2 out of 6). This clearly shows that tubular parameters were more affected by the radiolabelled peptides compared to the glomerular parameters. Further studies are needed to follow-up the consequences of using ^{177}Lu-DOTATATE in this group to evaluate their implications for long term tubular toxicity. The renal toxicity with 90-Yttrium based PRRT is approximated to be more profound than that of 177-Lu based PRRT (*9, 10*). In all our cases ^{177}Lu based PRRT was used for therapy safely with no associated nephrotoxcity emphasizing the safe renal profile of ^{177}Lu based PRRT.

Conclusion:

Overall our preliminary results (based upon retrospective data analysis) with at least 3-5 cycles of PRRT show that in patients of NET with single functioning kidney, 177-Lu DOTATATE based PRRT administration along with proper renal protection and dose fractionation is feasible with no acute or chronic renal toxicity observed on follow-up. Further prospective studies are warranted (i) to assess the renal dosimetry and (ii) the long term renal consequences of the changes in ERPF observed in these patients.

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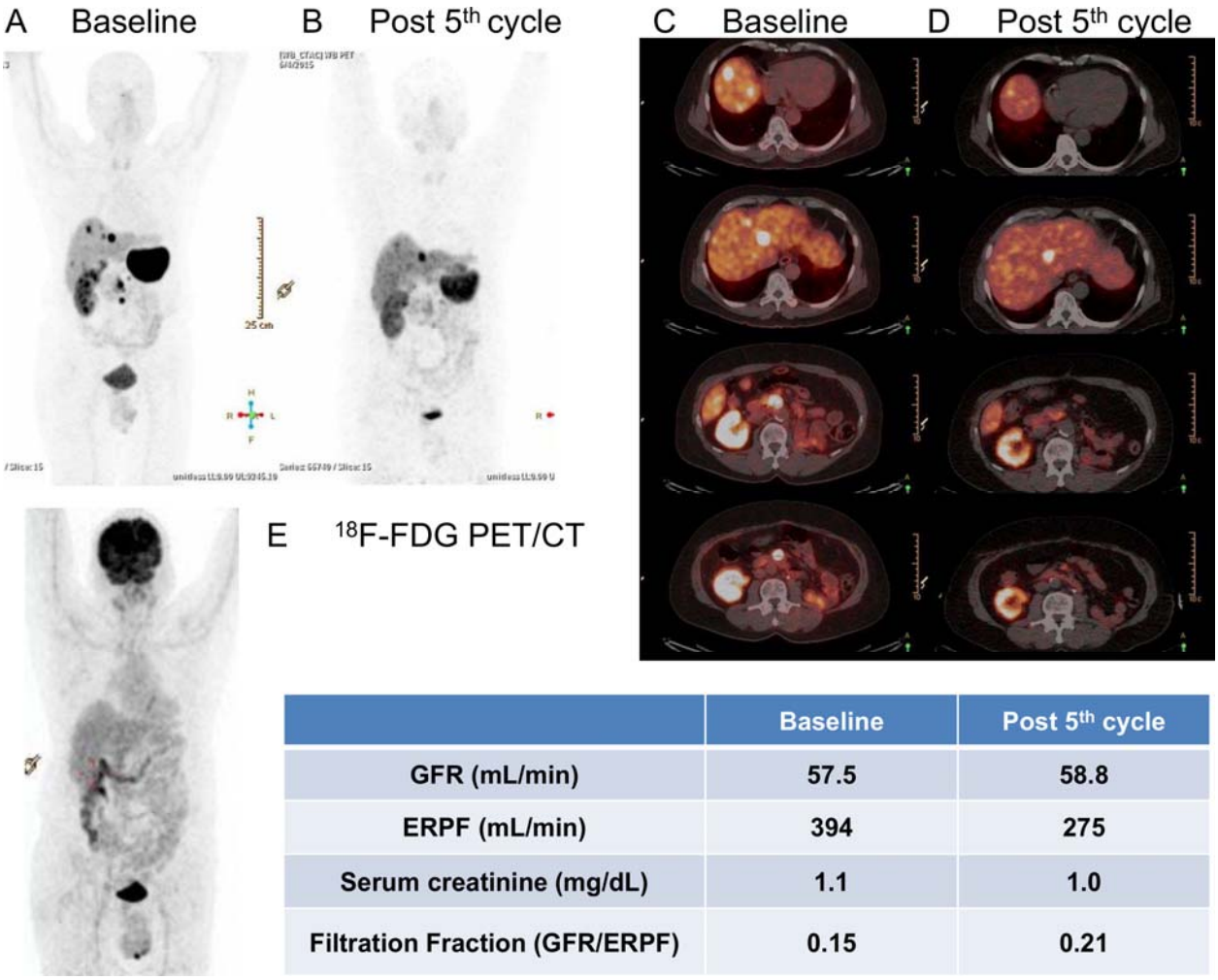

	Baseline	Post 5th cycle
GFR (mL/min)	57.5	58.8
ERPF (mL/min)	394	275
Serum creatinine (mg/dL)	1.1	1.0
Filtration Fraction (GFR/ERPF)	0.15	0.21

Fig 1. 62 year old male, who initially presented with abdominal pain and had a CT scan documented mesentric mass which following excision was found to be well diffrentiated NET on HPR. The patient also had history of renal cell carcinoma of left kidney and had undergone left nephrectomy. After a disease free period of 4 years, the patient present with disease recurrence with ^{68}Ga-DOTATATE PET/CT showing SSTR expressing lesions in segment IV and segment VIII with few peripancreatic nodules **(Fig 1A and 1C)**. ^{18}F-FDG PET/CT was normal **(Fig 1E)**. The patient has undergone 5 cycles of ^{177}Lu based PRRT. Post 5th cycle PRRT ^{68}Ga-DOTATATE PET/CT **(Fig 1B and 1D)** showed almost complete resolution of seg VIII and peripancreatic lesions with only seg IV lesion seen. Overall treatment response assessment was good partial response.

Post 5 cycles no acute renal toxicity was seen but grade I chronic renal toxicity was observed, he had same grade I chronic renal toxicity before PRRT being undertaken. Baseline filtration fraction of 0.15 (rounded off) increased to 0.21 following five cycles of therapy due to reduction in ERFP compared to GFR (which was stable in this example).

Table 1. Patient characteristics

Age Distribution:	33-63
Sex: (Male: Female)	3:3
Histology: (Well differentiated: Intermediate: Poorly Differentiated)	2:2:2
Site of primary: Pancreas Kidney Ureter Unknown Primary Ileum	2 1 1 1 1
Number of Metastasis: >5 <5	5 1
Functioning Kidney: (Right :Left)	(5:1)

Table 2. The causes for single functioning kidney and summary of biochemical tumor marker parameter (baseline and final analysis) in each individual

Patient	Cause for single functioning kidney	Biochemical response : S Cg A (ng/ml)
Case I	The pancreatic body and tail lesion extends into the left adrenal and left kidney rendering the kidney non functional	334—>102
Case II	Incidentally detected non functioning left kidney during workup for PRRT.	2600—>2420
Case III	Horse shoe kidney NET. Partial nephrectomy for removal of primary.	962—>97.97
Case IV	Previous history of Left renal cell carcinoma. Nephrectomy done for same.	866.7 —>808.76
Case V	Left ureter NET. Left kidney non-functional due to the ureteric lesion from time of diagnosis.	68.10—>37.9
Case VI	Right kidney is polycystic dysplastic. Recognized at time of workup of PRRT.	435.75—>131.3

Table 3. The indications for PRRT and the grade of tracer uptake on diagnostic pre-treatment evaluation scan

Patient	Symptoms at presentation and reason for starting PRRT	Grade of HYNIC/Gallium uptake:
Case I	Severe abdominal pain and backache. Not relieved by pain killers and long acting octreotide injections.	Grade IV
Case II	Severe abdominal pain and backache. Not relieved by pain killers and long acting octreotide injections.	Grade IV
Case III	Severe abdominal pain and vomiting. Not relieved by pain killers and long acting octreotide injections.	Grade IV
Case IV	Severe diarrhoea and episodes of flushing. Not relieved by long acting octreotide injections.	Grade IV
Case V	Severe abdominal pain and loss of appetite. Pelvic mass recurrence post operative unresectable.	Grade III
Case VI	Severe abdominal pain, vomiting, diarrhoea and backache. Not relieved by pain killers and long acting octreotide injections.	Grade IV

Table 4. Risk Factors

	Hypertension	Diabetes	Cisplatin based Chemotherpy	Capecitabine based Chemotherpy
Case I	-	-	-	-
Case II	-	+	+++	-
Case III	-	-	+++	-
Case IV	-	-	-	-
Case V	+	-	-	-
Case VI	-	-	-	+++

For Hypertension and Diabetes : + indicates presence of concerning clinical condition for more than 10 yrs. – indicates absence of the concerning clinical condition.

For chemotherapy : + indicates receiving of 2 cycles of nephrotoxic chemotherapy, - indicates no chemotherapy

Table 5. Overall Renal Toxicity Profile

	Number of cycles of PRRT given with cumulative activity	Number of months of Follow up	Acute Renal toxicity	Chronic Renal toxicity
Case I	3(16.6 GBq)	12	-	-
Case II	3(16.6 GBq)	12	-	-
Case III	5(36.2 GBq)	56	-	++
Case IV	5(36.2 GBq)	25	-	+
Case V	3(16.6 GBq)	15	-	-
Case VI	4(24.1 GBq)	24	-	+

Table 6. Renal Toxicity Profile as per individual cycle of PRRT

	PRRT Cycle	Number of months of Follow up	Acute Renal toxicity	Chronic Renal toxicity
Case I	Baseline	3	-	-
	1st cycle of PRRT	8	-	-
	2nd cycle of PRRT	12	-	-
	3rd cycle of PRRT			
Case II	Baseline	3	-	-
	1st cycle of PRRT	8	-	+
	2nd cycle of PRRT	12	-	-
	3rd cycle of PRRT			
Case III	Baseline	56	-	++
	1st cycle of PRRT		-	+++
	2nd cycle of PRRT		-	++
	3rd cycle of PRRT		-	++
	4th cycle of PRRT		-	++
	5th cycle of PRRT		-	++
Case IV	Baseline	3	-	++
	1st cycle of PRRT	8	-	++
	2nd cycle of PRRT	14	-	+
	3rd cycle of PRRT	20	-	-
	4th cycle of PRRT	25	-	+
	5th cycle of PRRT		-	+
Case V	Baseline	3	-	-
	1st cycle of PRRT	8	-	+
	2nd cycle of PRRT	15	-	-
	3rd cycle of PRRT		-	-
Case VI	Baseline	3	-	++
	1st cycle of PRRT	10	-	++
	2nd cycle of PRRT	17	-	++
	3rd cycle of PRRT	24	-	+
	4th cycle of PRRT			

Table 7. Percentage reduction in the GFR and ERPF following PRRT and corresponding change in filtration fraction

	Number of cycles of PRRT given	Number of months of Follow up	% decrease in GFR from baseline	% decrease in ERPF from baseline	Increase in Filtration fraction from baseline
Case I	3	12	13.8	20.7	0.23 to 0.24
Case II	3	12	5.3	31.4	0.17 to 0.24
Case III	5	56	-	2.8	0.49 to 0.55
Case IV	5	25	-	30.2	0.15 to 0.21
Case V	3	15	-	-	
Case VI	4	24	-	-	