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Original article

^{177}Lu-DOTATATE Peptide Receptor Radionuclide Therapy in Patients with Borderline Low and Discordant Renal Parameters: Treatment Feasibility Assessment by Sequential Estimation of Triple Parameters and Filtration Fraction

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Abstract

The aim was to assess the effect of standard fixed-dose protocol of ^{177}Lu-DOTATATE peptide receptor radionuclide therapy (PRRT) in patients with borderline low renal function of one parameter (glomerular filtration rate [GFR], effective renal plasma flow [ERPF] or serum creatinine), that was discordant with the remaining parameters and determine the feasibility of this procedure in this group of patients. Renal toxicity of PRRT is a routine issue or concern for such cases. We compared different renal parameters used for pretherapy assessment in patients with borderline low single parameter at baseline and their potential significance with regards to deterioration of renal function subsequently. A retrospective analysis was performed in patients of metastatic neuroendocrine tumors who received therapeutic ^{177}Lu-DOTATATE (using standard fixed-dose protocol) and had borderline compromised renal parameter values (either of GFR/ERPF/serum creatinine). Filtration fraction (FF) was also estimated in each case and all renal parameters were correlated using kappa statistics. The characteristics of cases showing progressive worsening of renal function in the follow-ups were also studied. A total of 15 patients (11 males, 4 females; age range: 32–75 years) were selected among a population of 450 patients. The follow-up duration ranged from 10 to 48 months and administered cumulative activity ranged 9.9–31.3 GBq (2–5 cycles). Based on the parameter characteristics, the study population was divided into following four groups: (a) patients with reduced GFR and maintained ERPF and normal serum creatinine (n = 3); (b) patients with reduced ERPF with maintained GFR and borderline elevated/normal serum creatinine (n = 3); (c) patients with both reduced GFR and ERPF and maintained serum creatinine (n = 1); (d) patients with compromised single kidney function (n = 5). A total of four patients were found who had normal baseline renal function values but showed progressive worsening in the subsequent period. There was no significant change in renal parameters during the follow-up in both Groups a and c. Two patients of Group b demonstrated well-maintained other renal parameters, whereas in 1 patient, there was the evidence of renal toxicity with gradual fall of GFR and ERPF and progressive increase in serum creatinine level. In patients with compromised single kidney function at baseline (Group d), there was overall maintained normal renal parameters, whereas 3 of 5 (60%) showed the increase of FF of the affected kidney. Interestingly, a compensatory hyperfunction was noted in the contralateral kidney. PRRT with ^{177}Lu-DOTATATE is feasible and can be considered in patients with reduced GFR and with maintained ERPF and normal serum creatinine and also in the presence of single compromised parameter if the other two are normal; however, these patients need critical monitoring.

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Introduction

Peptide receptor radionuclide therapy (PRRT) is a novel targeted palliative therapy primarily employed for metastatic/advanced well differentiated neuroendocrine tumors (NETs) such as gastroenteropancreatic and pulmonary NETs, paragangliomas, neuroblastomas, pheochromocytomas, and medullary carcinoma of thyroid. The radiopharmaceuticals used for PRRT are yttrium-90 (^{90}Y)/lutetium-177 (^{177}Lu) – 1,4,7,10-tetraazacyclododecane (DOTA)-TATE/TOC/NOC. PRRT produces modest side effects as compared to other palliative therapies such as chemotherapy and radiotherapy. It has demonstrated encouraging results with in treating patients of metastatic or inoperable NET. However, the radiolabeled SSA analogs are reabsorbed in proximal convoluted tubules of nephrons, which may cause adverse effects on kidneys.[1-3] The other documented but well-managed side effects during or following the treatment are nausea, vomiting, fatigue, pain abdomen, hormonal crisis, and temporary worsening of the symptoms noted in patients with tumors that produce a large amount of hormones, slight decrease in the number of blood cells (temporary). The most common side effects of amino acid infusion are nausea, vomiting and hyperkalemia (K^+ >5.0 mmol/L); the nausea and vomiting can be well managed with the combination of ondansetron and dexamethasone in most cases. The long-term side effects of PRRT include renal compromise and bone marrow toxicity.

As a part of the pretreatment evaluation as well as to assess the renal toxicity of the administered therapy, pretherapy serum creatinine and renal scintigraphy with glomerular and tubular agents (^{99m}Tc-DTPA and ^{99m}Tc-EC renogram) are performed. This is followed by evaluation of serum creatinine during follow-up posttherapy. Among the renal scintigraphy procedures, glomerular filtration rate (GFR) fraction and effective renal plasma flow (ERPF) are evaluated and suggested cut-off value stated is at least around 60% of age adjusted normal values.[4] Positively charged amino acids such as L-lysine and/or L-arginine, on co-administration, significantly reduce renal toxicity by competitively inhibiting re-absorption of radio-peptides in proximal tubules, thus reducing the uptake by 40%.[5] Plasma expander like Gelofusine, has also been employed, which when co-injected with lysine has shown to reduce the radio-peptide uptake by 62%–70%.[6,7] Despite the use of the aforementioned preventive measures, there can still be deterioration of renal function postPRRT, with an approximate loss of creatinine clearance 3.8% and 7.3%/year for ^{177}Lu-DOTATATE and ^{90}Y-DOTATOC, respectively.[8] In clinical practice during pretherapy work-up, one comes across a group of patients, who present with borderline low renal function as per one of these parameters, whereas the other two parameters are within normal limits: Not infrequently, in view of the fact that in the presence of extensive disease burden from NETs, PRRT constitutes a very important therapy, the attending physician needs to make a critical decision in these patients whether PRRT could be administered without denying therapy in needy patients.

Materials and Methods

Patients and study design

A retrospective analysis was performed on patients of metastatic NETs with borderline compromised discordant renal parameter of one type (either serum creatinine/GFR/ERPF) and normal values of the other two, who had received therapeutic ^{177}Lu-DOTATATE in view of advanced metastatic disease burden. The objective of this analysis was to assess the effect of the PRRT in this particular group of patients and determine feasibility of this procedure.

The standard PRRT protocol was followed for all patients such as (i) diagnosis of NET was confirmed in these patients by histopathology; (ii) availability of tumor/biochemical markers (serum chromogranin A and 24 h urinary 5-hydroxyindoleacetic acid) and (iii) functional imaging supportive of a NET (high uptake on ^{68}Ga-DOTATATE scan) and cross-sectional (computed tomography/magnetic resonance imaging) imaging information. The GFR and ERPF were estimated by ^{99m}Tc-DTPA and ^{99m}Tc-EC renogram respectively and same method and gamma camera was used for the follow-up evaluation.

Selection of patients for the study analysis

Patients with compromised renal parameters (either found to have decreased GFR or ERPF values or with elevated serum creatinine) and underwent minimum of two cycles of PRRT were included in this study. A total of 15 patients (11 males, 4 females) were found among a population of 450 patients.

Results

Patient characteristics

The patients' characteristics with the primary site of NET with metastases (if any) and details of therapy

administered during each cycle of PRRT are summarized in Table 1. The age group of the patients ranged from 32 to 75 years with male to female ratio of 3:1. The duration of follow-up ranged from 10 to 48 months and the cumulative activity administered ranged from 9.9 to 31.3 GBq (2–5 cycles of therapy given).

The patients' renal function parameters (serum creatinine, GFR, and ERPF), the filtration fraction (FF) (GFR/ERPF) and the response of these parameters in the follow-up course were tabulated. The patients were divided into sub-groups depending on the compromised renal parameter and are summarized in Tables 2-6.

Table 1: Patient characteristics

Serial number	Age (years)/sex	Histopathological characterization	Primary lesion site	Activity (MBq)
1	66/male	Well differentiated NET of lung (MIB-1: 2%-3%)	NET of right lung with multiple liver metastases	Total 3# 1#: 6882 2#: 6808 3#: 5513
2	46/male	Neuroendocrine carcinoma (Ki 67: 15%)	Left lower ureteric NET with perineural invasion	Total 4# 1#: 4736 2#: 5254 3#: 6882 4#: 5513
3	32/female	Well differentiated NET, Grade II (MIB-1: 8%)	NET of body of pancreas with liver metastases	Total 2# 1#: 5513 2#: 5106
4	52/female	Poorly differentiated NET of rectum, (MIB-1: 3%-4%)	Poorly differentiated NET of rectum	Total 3# 1#: 5735 2#: 5513 3#: 5032
5	51/male	Well differentiated NET of pancreas	Well differentiated NET of tail of pancreas with liver metastasis	Total 5# 1#: 7363 2#: 6179 3#: 5587 4#: 6475 5#: 5698
6	53/male	MEN I syndrome; Well differentiated NET (mediastinum), atypical carcinoid of thymus, NET pancreas	NET of thymus and pancreas	Total 5# 1#: 2442 2#: 4958 3#: 5439 4#: 5994 5#: 7807
7	61/male	Well differentiated NET (MIB-1: <1%)	Well differentiated NET of ileum with mesenteric deposits and liver metastasis	Total 3# 1#:5624 2#: 5069 3#: 5846
8	43/female	Well differentiated NET (MIB-1: <1%)	NET of horseshoe kidney with skeletal and liver metastasis	Total 4# 1#: 7400 2#: 7400 3#: 7400 4#: 6771
9	66/female	Metastatic poorly differentiated NET, Grade III (MIB-1: 20%)	Metastatic NET of liver with unknown primary	Total 4# 1#: 8066 2#: 6623 3#: 5957 4#: 6179
10	47/male	Well differentiated NET, Grade II (MIB-1: 15%)	NET of lung with mets to liver	Total 2# 1#: 5032 2#: 6216
11	75/male	Intermediate grade NET (MIB-1: 3%)	Metastatic NET of unknown primary with liver and skeletal metastases	Total 3# 1#: 6364 2#: 5254 3#: 5661

Contd...

Table 1: Contd...

Serial number	Age (years)/sex	Histopathological characterization	Primary lesion site	Activity (MBq)
12	55/male	Well differentiated NET, Grade II (MIB-1: 3%-4%)	Well differentiated pancreatic NET	Total 2# 1#: 5920 2#: 5883
13	63/male	Poorly differentiated neuroendocrine carcinoma	Inoperable mesenteric mass NET	Total 2# 1#: 7178 2#: 7548
14	66/male	Glucagonoma	Glucagonoma of pancreas with liver metastasis	Total 3# 1#: 5883 2#: 6142 3#: 5809
15	72/male	Well differentiated NET, Grade II (MIB-1: 4%-5%)	Mesenteric NET (carcinoid)	Total 2# 1#: 5032 2#: 4958

NET: Neuroendocrine tumour

Table 2a: Patients with reduced glomerular filtration rate and maintained effective renal plasma flow and normal serum creatinine

Patient number	Number of PRRT cycles	Serum creatinine (mg/dl)	GFR			ERPF			FF=GFR/ERPF
			Right	Left	Total	Right	Left	Total	
1	Pretherapy	1.05	32.6	22.2	54.8	177.5	149.6	327.1	0.16
	Post 1#	1.4	33.1	16.9	50.0	142.6	100.3	242.9	0.20
	Post 2#	1.21	24.04	18.2	42.24	210.8	155.0	365.8	0.11
	Post 3#	1.04	32.43	21.68	54.11	126.7	83.1	209.8	0.25
11	Pretherapy	0.9	26.9	22.5	49.4	179.18	147.11	329.29	0.15
	Post 1#	0.8	33.68	39.14	55.9	136.21	145.0	281.1	0.25
	Post 2#	0.9	32.1	35.6	56.8	154.96	146.16	301.12	0.22
	Post 3#	0.8	17.1	18.0	56.5	159.09	182.47	341.55	0.10
15	Pretherapy	1.1	24.69	22.32	47.01	213.2	203.9	417.25	0.11
	Post 1#	1.3	31.73	26.94	58.68	161.31	167.23	328.54	0.17
	Post 2#	1.3	21.83	22.11	43.94	183.79	148.93	332.72	0.13

GFR: Glomerular filtration rate; ERPF: Effective renal plasma flow; FF: Filtration fraction

Table 2b: Patients with reduced glomerular filtration rate and maintained effective renal plasma flow and normal serum creatinine (average values of parameters)

	Serum creatinine	Total ERPF	FF
Pretherapy	1.016667	357.8633	0.14
Post 1	1.166667	284.18	0.206667
Post 2	1.136667	333.2133	0.153333
Post 3	0.92	275.675	0.175

ERPF: Effective renal plasma flow; FF: Filtration fraction

Observation

There were a total of three patients with reduced GFR and borderline ERPF and serum creatinine were considered for PRRT in view of the patients' clinical status and a good symptomatic response was observed without any significant change in renal parameters during the follow-up [Figure 1a-c].

A total of three patients with reduced ERPF and borderline elevated/normal serum creatinine but with maintained GFR were found. Of three patients, two patients demonstrated well-maintained all renal parameters with no significant toxicity noted subsequently, whereas in one patient there was renal toxicity found with gradual fall of GFR and ERPF and progressive increase in serum creatinine levels [Figure 2a-c].

In one patient, we had given PRRT with reduced both GFR and ERPF, but patient had normal serum creatinine. This patient had subsequently shown good symptomatic response without any significant renal toxicity and well maintained renal parameters in the follow-up period [Figure 3].

In five patients, we found single kidney compromised function and opposite kidney is well functioning with overall maintained renal parameters. In this group, we observed a stable or maintained renal parameter after the PRRT without any significant renal toxicity. We separately assessed the FF of compromised single kidney, in which we observed a significant increase of FF when compared to total

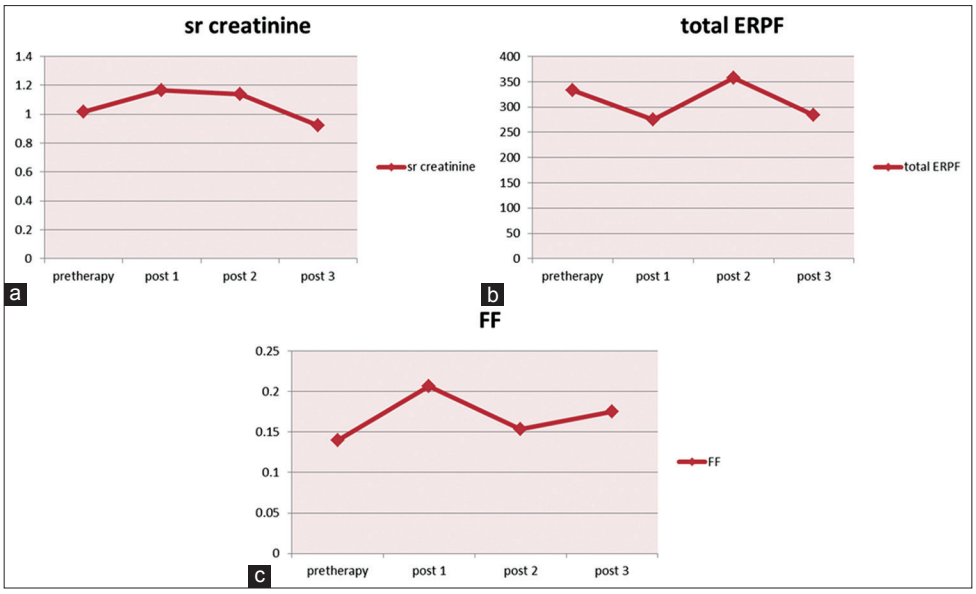

Figure 1: (a-c) Plotted average values of serum creatinine, total effective renal plasma flow and filtration fraction with each cycle of peptide receptor radionuclide therapy

Table 3a: Patients with reduced effective renal plasma flow with maintained glomerular filtration rate and borderline elevated/normal serum creatinine

Patient number	Number of PRRT cycles	Serum creatinine (mg/dl)	GFR			ERPF			FF=GFR/ERPF
			Right	Left	Total	Right	Left	Total	
5	Pretherapy	1.8	33.7	37.0	70.7	116.0	153.6	269.7	0.26
	Post 1#	1.5	26.68	33.16	60.03	112.47	159.38	271.85	0.22
	Post 2#	1.46	29.58	41.14	70.72	112.65	143.65	256.11	0.27
	Post 3#	1.25	41.21	42.18	83.4	147.5	186.83	334.33	0.24
	Post 4#	1.28	37.36	38.95	76.31	99.8	116.5	216.2	0.35
	Post 5#	1.32	29.96	31.15	61.11	115.61	127.28	242.89	0.25
6	Pretherapy	1.3	27.76	29.1	56.87	134.75	128.21	262.96	0.21
	Post 1#	1.38	48.7	27.62	76.32	116.2	98.41	214.6	0.35
	Post 2#	1.31	30.26	28.59	58.85	143.58	132.97	276.56	0.21
	Post 3#	1.4	37.21	31.91	69.11	153.55	131.13	284.68	0.24
	Post 4#	1.42	34.9	28.65	63.55	139.52	132.35	271.87	0.23
	Post 5#	1.3	28.59	23.74	52.33	115.69	120.27	235.95	0.22
10	pretherapy	1.15	42.63	31.24	73.87	148.83	110.17	259.01	0.28
	Post 1#	1.2	26.98	14.78	41.75	175	118.3	293.3	0.14
	Post 2#	1.44	13.94	10.21	24.15	113.63	84.41	198.04	0.12

GFR: Glomerular filtration rate; ERPF: Effective renal plasma flow; FF: Filtration fraction

Table 3b: Patients with reduced effective renal plasma flow with maintained glomerular filtration rate and borderline elevated/normal serum creatinine (average values of parameters)

	Serum creatinine	Total ERPF	FF
Pretherapy	1.416667	67.14667	0.25
Post 1#	1.36	59.36667	0.236667
Post 2#	1.403333	57.90667	0.2
Post 3#	1.325	76.255	0.24
Post 4#	1.35	69.93	0.29
Post 5#	1.31	115.65	0.235

ERPF: Effective renal plasma flow; FF: Filtration fraction

FF of the affected kidney in 3 out of 5 patients (60%) and appeared similar in the remaining 2 patients [Figure 4a-c].

Renal toxicity as observed in four patients where we noted progressive reduction of all the parameters in the follow-up period (in baseline and at least two subsequent values). Subsequent cycle of PRRT was denied in these patients and referred patients for the other modes of palliative therapy. Interestingly, 3 out of 4 (i.e. 75%) had all parameters normal at baseline and 1 out of 4 had reduced ERPF and normal GFR and serum creatinine at baseline [Figure 5].

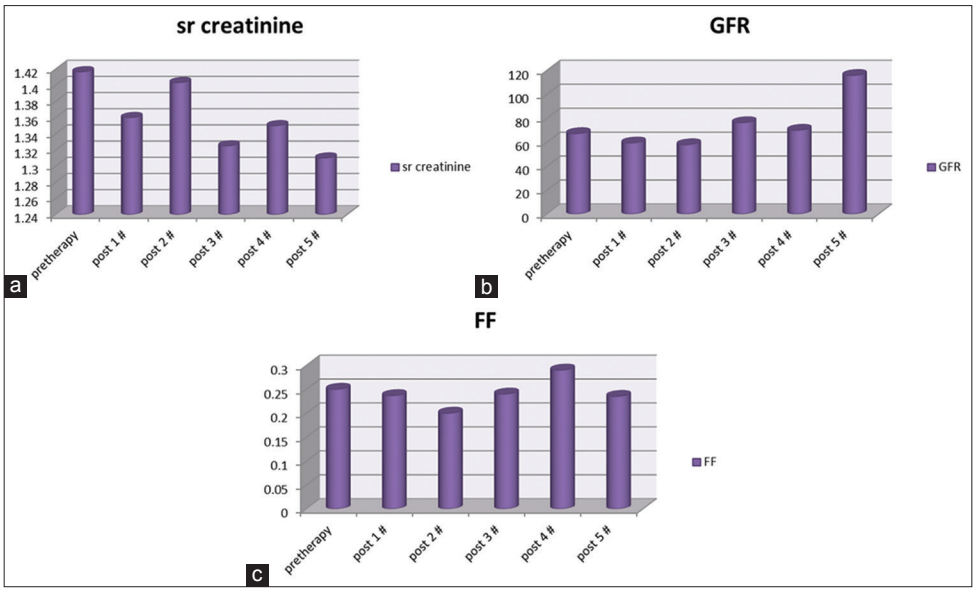

Figure 2: (a-c) Plotted average values of serum creatinine, total glomerular filtration rate and filtration fraction with each cycle of peptide receptor radionuclide therapy

Table 4a: Patient with reduced both glomerular filtration rate and effective renal plasma flow and maintained serum creatinine

Patient number	Number of PRRT cycles	Serum creatinine (mg/dl)	GFR			ERPF			FF=GFR/ERPF
			Right	Left	Total	Right	Left	Total	
12	Pretherapy	1.1	25.6	16.4	42.0	144.4	116.3	260.8	0.16
	Post 1#	1.1	30.95	25.37	56.33	94.06	78.2	172.26	0.32
	Post 2#	1.0	22.26	18.06	40.31	82.59	106.68	189.27	0.21

GFR: Glomerular filtration rate; ERPF: Effective renal plasma flow; FF: Filtration fraction

Table 4b: Patient with reduced both glomerular filtration rate and effective renal plasma flow and maintained serum creatinine (average values of other parameters with each cycle)

	Serum creatinine	FF
Pretherapy	1.1	0.16
Post 1#	1.1	0.32
Post 2#	1	0.21

FF: Filtration fraction

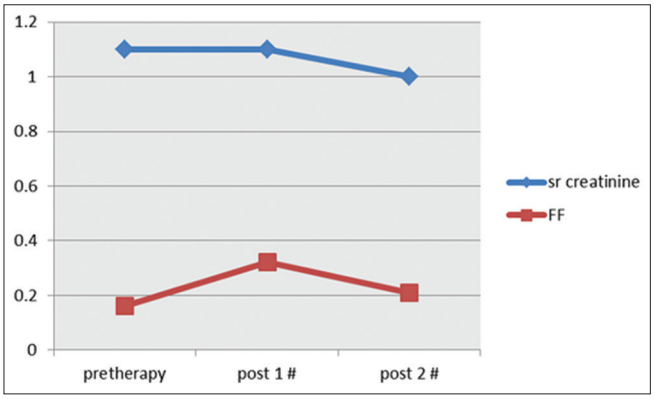

Figure 3: Plotted average values of serum creatinine and filtration fraction with each cycle of peptide receptor radionuclide therapy

Statistical methods

We correlated all four renal parameters using kappa statistics to estimate the agreement between these renal parameters individually with GFR as the gold standard. Interestingly, very poor concordance was noticed between GFR and other renal parameters in both pretherapy and posttherapy values. Kappa value more than 0.7 is an indicator of good agreement, which was not found in any of the renal parameters.

Discussion

Renal toxicity in PRRT mainly arises from the re-absorption of the radio-peptide in the proximal convoluted tubules of nephrons and the resulting retention of radio-peptide in the renal parenchyma. Nephrotoxicity is markedly noted after (^{90}Y-DOTA 0, Tyr 3)-octreotide as compared to ^{177}Lu-DOTATATE due to the high energy and longer range of beta particle tissue penetration of ^{90}Y (Emax: 2.27 MeV, Rmax: 11 mm); ^{177}Lu, whose beta particles possess lower energy and shorter tissue penetration (Emax: 0.49 MeV, Rmax: 2 mm).[9]

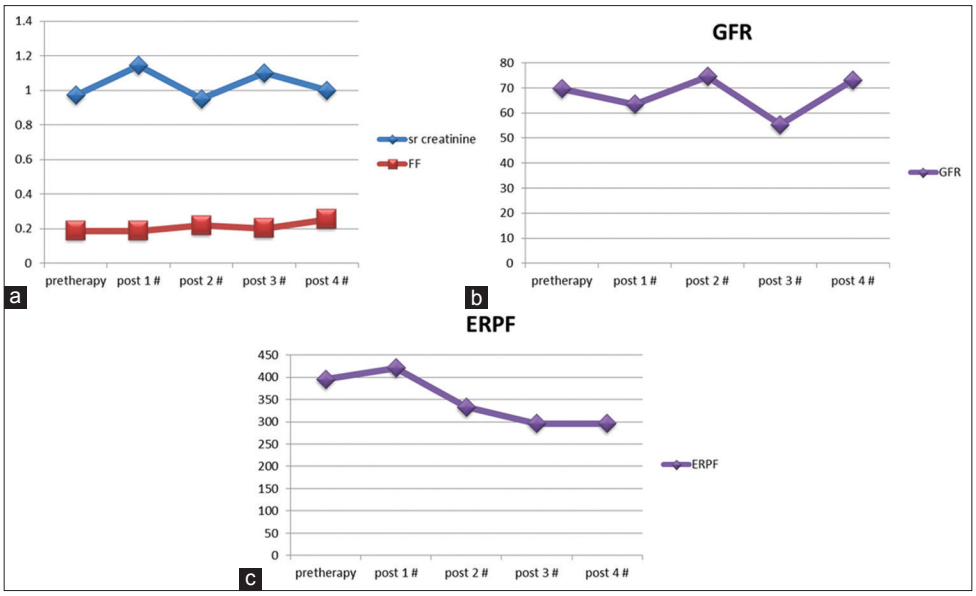

Figure 4: (a-c) Plotted average values of serum creatinine, total glomerular filtration rate, effective renal plasma flow, and filtration fraction with each cycle of peptide receptor radionuclide therapy in patients with single compromised kidney

Table 5a: Patients with compromised single kidney function

Patient number	Number of PRRT cycles	Serum creatinine (mg/dl)	GFR			ERPF			FF=GFR/ERPF	FF of deranged single kidney
			Right	Left	Total	Right	Left	Total		
2	Pretherapy	1.3	65.2	22.2	87.4	322.1	51.27	373.4	0.23	0.43
	Post 1#	1.4	55.3	20.3	75.6	433.2	75.5	508.7	0.14	0.26
	Post 2#	1.08	69.9	18.3	88.2	401.2	71.1	472.3	0.18	0.25
	Post 3#	1.3	69.5	13.1	82.6	374.08	56.27	430.35	0.19	0.23
	Post 4#	1.0	90.45	18.94	109.38	401.21	63.83	465.04	0.23	0.29
3	Pretherapy	0.96	19.08	57.4	76.48	118.52	240.98	359.46	0.21	0.16
	Post 1#	0.82	29.3	55.71	85.02	91.65	241.45	333.1	0.25	0.31
	Post 2#	0.58	43.8	60.9	104.7	138.07	186.96	325.03	0.32	0.31
4	Pretherapy	0.9	50.83	19.53	70.36	445.2	28.4	473.6	0.14	0.68
	Post 1#	1.1	68.36	10.43	78.79	279.35	17.56	296.95	0.26	0.59
	Post 2#	1.0	63.65	14.04	77.69	321.3	24.3	345.6	0.22	0.57
	Post 3#	1.1	55.11	8.73	63.85	255.35	17.09	272.43	0.23	0.51
7	Pretherapy	1.1	14.87 (ectopic)	55.13	67.69	62.25	314.38	376.3	0.17	0.23
	Post 1#	1.4	7.21	51.34	58.56	88.5	456.6	545.1	0.10	0.08
	Post 2#	1.2	14.1	55.2	69.4	56.18	274.74	330.92	0.20	0.25
	Post 3#	1.0	8.6	41.3	49.9	69	323.57	392	0.12	0.12
8	Pretherapy	0.6	14.4	31.82	46.22	-	-	-	-	-
	Post 1#	1.0	4.6	15.01	19.68	-	-	-	-	-
	Post 2#	0.9	14.8	18.0	32.8	41.9	149.4	191.3	0.17	0.35
	Post 3#	1.0	7.3	17.5	24.8	29.2	61.7	90.9	0.27	0.25
	Post 4#	1.0	12.3	24.4	36.8	27.9	99.6	127.5	0.28	0.44

GFR: Glomerular filtration rate; ERPF: Effective renal plasma flow; FF: Filtration fraction

Table 5b: Patients with compromised single kidney function (average values of parameters with each cycle)

	Serum creatinine	FF	GFR	ERPF
Pretherapy	0.972	0.1875	69.63	395.69
Post 1#	1.144	0.1875	63.53	420.8875
Post 2#	0.952	0.218	74.558	333.03
Post 3#	1.1	0.2025	55.2875	296.42
Post 4#	1	0.255	73.09	296.27

GFR: Glomerular filtration rate; ERPF: Effective renal plasma flow; FF: Filtration fraction

Various institutes consider various parameters as per their institutional protocol and the resources available at that time and place. GFR (calculated by camera based GATES method) using ^{99m}Tc-DTPA is presently the most commonly used parameter for pretherapy evaluation of the renal function. Some centers use ERPF (using ^{99m}Tc-MAG3/EC) as the baseline pretherapy renal parameter in addition to serum creatinine. At our center, we usually assess all three parameters mentioned above for the

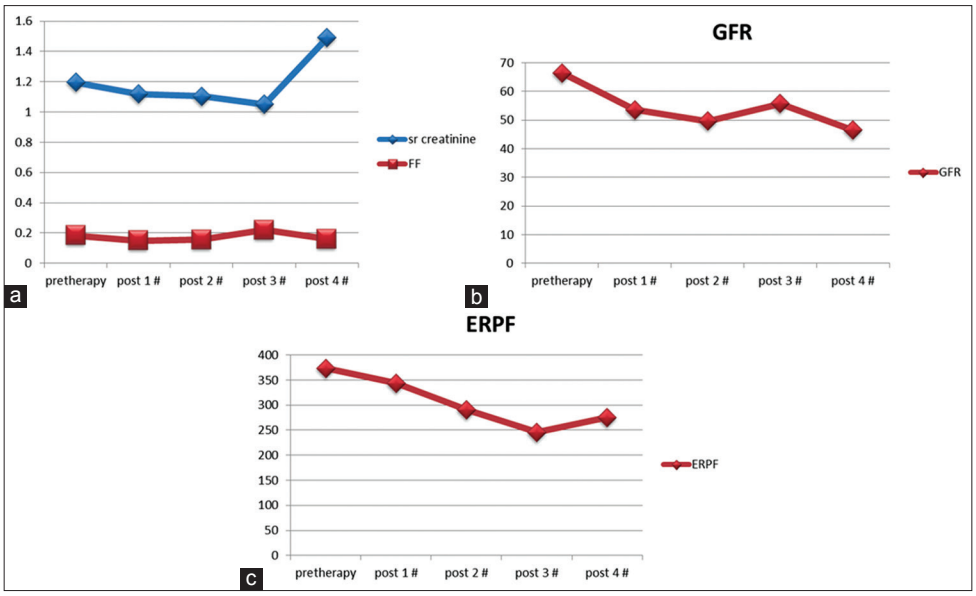

Figure 5: (a-c) Plotted average values of serum creatinine, total glomerular filtration rate, effective renal plasma flow and filtration fraction with each cycle of peptide receptor radionuclide therapy

Table 6a: Parameter characteristics of patients with demonstrated renal toxicity

Patient number	Number of PRRT cycles	Serum creatinine (mg/dl)	GFR			ERPF			FF=GFR/ERPF
			Right	Left	Total	Right	Left	Total	
9	Pretherapy	1.30	54.1	36.7	90.9	321.9	231.1	553	0.16
	Post 1#	1.3	49.3	27.0	76.3	257.9	196.9	454.8	0.16
	Post 2#	1.08	52.85	37.9	90.75	255.5	161	417.35	0.21
	Post 3#	1.1	38.84	28.5	67.3	148.2	105.8	254	0.26
	Post 4#	1.49	25.78	20.7	46.48	160.9	114.38	275.24	0.16
10	Pretherapy	1.15	42.63	31.24	73.87	148.83	110.17	259.01	0.28
	Post 1#	1.2	26.98	14.78	41.75	175	118.3	293.3	0.14
	Post 2#	1.44	13.94	10.21	24.15	113.63	84.41	198.04	0.12
13	Prertherapy	1.1	33.5	29.6	63.22	199.19	171.17	370.36	0.17
	Post 1#	1.5	33.46	27.94	61.4	168.16	161.16	359.33	0.17
	Post 2#	1.4	20.25	16.99	37.23	121.31	121.04	242.04	0.15
14	Pretherapy	0.8	34.54	26.73	61.27	238.81	217.0	455.8	0.13
	Post 1#	0.8	31.9	20.8	52.7	210.7	171.2	381.3	0.13
	Post 2#	0.9	34.78	22.84	57.63	206.8	181.3	381.8	0.15
	Post 3#	1.0	22.85	21.37	44.22	103.7	133.9	237.6	0.18

GFR: Glomerular filtration rate; ERPF: Effective renal plasma flow; FF: Filtration fraction

Table 6b: Parameter characteristics of patients with demonstrated renal toxicity (average values of parameters with each cycle)

	Serum creatinine	FF	GFR	ERPF
Pretherapy	1.196	0.184	66.43	373.252
Post 1#	1.12	0.15	53.604	344.102
Post 2#	1.104	0.156	49.612	291.126
Post 3#	1.05	0.22	55.76	245.8
Post 4#	1.49	0.16	46.48	275.24

GFR: Glomerular filtration rate; ERPF: Effective renal plasma flow; FF: Filtration fraction

pretherapy renal function assessment before each cycle, as well as post-PRRT for the toxicity profile assessment. FF, which is the ratio of GFR to ERPF, was also used to observe the relative change of one parameter more than the other and was compared with the baseline values. This would clarify whether the tubular function is more affected compared to the glomerular function, which is theoretically predicted by the behavior of the radiopharmaceutical.[10]

Thus, in the present study, we compared and observed the change in serum creatinine, GFR, ERPF and FF pretherapy and posttherapy. Most of the center considered GFR as the main renal parameter for pretherapy assessment. There was not much concordance or agreement noted between these renal parameters with kappa statistics (must be more than 0.7 for the agreement to be significant).

We included few cases with reduced GFR but with maintained ERPF (>300) and serum creatinine (<1.4 mg/dl) values, and hence we considered this group of patients for PRRT and we found good symptomatic response without any significant renal toxicity in the subsequent cycles of PRRT. We also considered few patients for PRRT in which we found raised serum creatinine but with maintained GFR and a patient with reduced both GFR and ERPF with maintained serum creatinine; however, in all these cases, we found good tolerance for PRRT without any significant renal toxicity.

It is however important to perceive that whilst Tc-99m DTPA does measure GFR, Tc-99 m EC does not accurately measure EPRF, this can only be measured using I-125 hippuran or similar. As 99 mTc-EC is both filtered and excreted in variable amounts between patients it is at times very unreliable, this is even more inaccurate of there is any disassociation of the Tc-99 m from the EC. Furthermore, there is no clear evidence that changes in ERPF have any definitive predictive value, the options are (a) stick to GFR, or (b) include the Tc-99 m EC data, but make this clear, it does equate with ERPF and the significance of its early change is unknown at present.

We studied five cases where there was significant deranged function of one kidney and compensatory hyper function noted in the contra lateral kidney, we considered for PRRT as the age adjusted GFR was more than 60% (as per IAEA and EANM guidelines) and serum creatinine within normal limits. We noted a maintained kidney function in this group of patients in the subsequent PRRT cycles without any overall renal compromise.

Renal toxicity was noted in few patients, who was studied separately [Table 6], for whom the follow-up therapy was not considered and was referred for the other modes of treatment. No hematological toxicity was noted in any of the above patients who were considered in this study.

Conclusion

Renal toxicity is most common long term complication of PRRT that warrant pretherapy renal function evaluation necessary in all cases. From the present analysis, we can conclude that in patients with compromised single renal parameter, delivery of PRRT with ^{177}Lu-DOTATATE is possible, if we evaluate all renal parameters, that is, GFR, ERPF and serum creatinine combined.

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Conflicts of interest
There are no conflicts of interest.

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