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Intra-arterial ^{177}Lu-DOTATATE Therapy in Patients with Metastatic Neuroendocrine Tumours in Liver Dominant Disease "A Novel Theranostic Approach to Augment Therapeutic Potential": Feasibility and Safety Profile

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Abstract

Purpose: The aim of the study was to assess the feasibility, safety, tolerability and efficacy of intra-arterial infusion of ^{177}Lu-DOTATATE in patients with well differentiated liver dominant metastatic NET.

Method: Four patients with well differentiated grade II liver dominant neuroendocrine metastasis (Ki67 index ≤ 20%) were included in this study with ^{68}Ga-DOTANOC avid liver metastasis with or without extra hepatic disease. Each patient underwent intra-arterial (IA) administration of 7.4 GBq ^{177}Lu-DOTATATE through selective hepatic arterial catheterization, along with amino acid infusions over 4-6 hours at intervals of 8-12 weeks, with a total of 12 cycles (two patients received 4 cycles of IA infusion, third received only two cycles of IA infusion and the last one received 2 cycles IV followed by 2 IA cycles). All patients received 30 mg long acting octreotide (LAR) on day 5 of ^{177}Lu-DOTATATE therapy. Follow up imaging with ^{68}Ga-DOTANOC PET/CT whole body scan was done after 8 weeks of completion of the second and fourth cycles of ^{177}Lu-DOTATATE respectively and compared with baseline imaging to determine response to treatment. Complete blood counts including platelet counts were monitored on a weekly basis until they reached nadir levels. The clinical response, safety and toxicity profiles as well as tumor markers were assessed pre and post treatment, with a time frame of up to 3 months after last treatment.

Results: All patients tolerated the IA infusion of ^{177}Lu-DOTATATE therapy well, with none experiencing any significant procedure related acute side effects. None of the patients developed acute radiation induced liver disease or renal toxicity. Only one patient developed grade 1 to 2 hematological toxicity. Remaining others was stable with none developing severe grade 3 or 4 hematological toxicity. Only one patient developed transient increase of hepatic enzymes, which normalized subsequently with no decrease in the total bilirubin levels. None of them showed compromise in their quality of life, with a definite improvement in one of them. Two patients showed partial response to therapy according to RECIST criteria and patients showed stable disease. None of them had disease progression. All 4 patients reported significant improvement in symptoms and sense of well-being after treatment initiation. Concordant decrease in serum chromogranin A levels were seen in two patients. Although there was rise in the serum chromogranin A in one patient, he showed good partial radiological response, was asymptomatic, clinically well with no deterioration in his performance status.

Conclusion: Our initial experience of IA administration of ^{177}Lu-DOTATATE therapy in patients with liver dominant metastases is promising, feasible, safe and tolerable. The preliminary therapeutic potential of this therapy is encouraging. However, further prospective studies are needed to show its impact in improving clinical outcomes, median survival and progression free survival.

Keywords: ^{177}Lu-DOTATATE; PRRT; Intra-arterial infusion; Neuroendocrine liver metastases; Liver dominant disease

Introduction

Neuroendocrine tumors (NETs) are rare, slow growing tumors with increasing incidence over the past few years. The annual incidence of clinically significant NETs is approximately 2.5-5 per 100000 population with a prevalence of 35 per 100000 [1]. Tumors of the gastroenteropancreatic system (GEPNET) account for approximately 70% of cases, followed by respiratory tract tumors seen in 25% cases. In the recent years, there have been major changes in the understanding of the disease biology and its classification, with emergence of various treatment options. While surgery remains the mainstay of treatment in early localized well-differentiated NETs, most patients are often

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diagnosed later, presenting with inoperable or metastatic disease. In fact, 46% to 93% of NET patients, in particular up to 75% of GEPNET patients present with liver metastasis at the time of diagnosis [2,3]. These patients have a significantly worse prognosis than those without liver involvement, with 5-year survival of 0% to 20% [3,4]. Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE is a recognized targeted therapy for metastatic NETs, predominantly for grade I and grade II disease with encouraging results in a palliative setting [5-10]. ^{177}Lu-DOTATATE therapy has been approved in Europe in September 2017 and subsequently by US Food and Drug Administration (FDA) in January 2018 for treatment of somatostatin receptor (SSR) positive GEPNETs, including those of foregut, midgut and hindgut. The results of the phase 3 NETTER- 1 trial shows favourable outcomes with respect to the primary end point of progression free survival and other secondary objectives like overall survival, objective response rate and quality of life measures [5,11]. Despite the increased tumor response rates and progression free survival following PRRT, liver metastases still remains the major cause of morbidity and mortality in these patients who have a worse outcome in terms of overall survival after treatment with ^{177}Lu- DOTATATE compared to patients with limited or no liver metastases [2,4]. The standard treatment schedule consists of multiple cycles of intravenous (IV) administration of ^{177}Lu-DOTATATE. While the objective radiologic response with IV PRRT is observed in up to 30% of patients, in most cases it still has only a tumor stabilizing effect [7,8]. Few studies have reported enhanced lesion uptake by Intraarterial (IA) infusion of PRRT and its subsequent therapeutic potential [12-17]. It has been demonstrated that IA administration of ^{68}Ga-DOTA(0)-d-Phe(1)-Tyr(3)-octreotide (DOTATOC) results in a high first-pass effect [13,15]; with higher rate of objective radiologic response as observed with IA infusion of DOTATOC labelled therapeutic β emitters 90Y and 177Lu into the hepatic artery of 15 GEPNET patients with liver metastases and compares favorably with systemic chemotherapy and IV radio peptide therapy [12-17]. Since there is limited published literature on the use of PRRT by IA infusion, the aim of our study was to assess the feasibility, safety, tolerability and efficacy of IA ^{177}Lu-DOTATATE therapy in patients with well differentiated liver dominant metastatic NET.

Materials and Methods

Four patients with well differentiated grade II liver dominant neuroendocrine metastasis were included in this study (Table 1). Their histopathology and Ki67 index (≤ 20%) were verified. There were two patients with primary pancreatic, and one each of duodenal and bronchial carcinoid tumor. All patients had liver metastasis with or without extra hepatic disease, with measurable liver lesions and were tracer avid on SSR ^{68}Ga-DOTANOC PET-CT scintigraphy. Except for one patient who had an inoperable primary pancreatic NET, remaining three were post-operative cases who were receiving long acting octreotide at monthly intervals. Two of these patients had received chemotherapy (Capacetabine and Temozolamide regime) and developed disease progression and hence were referred for PRRT. Informed consents were taken from all patients. Baseline investigations included complete blood counts, liver function test, renal function test, coagulation profile and serum chromogranin A levels within 2 weeks of the first treatment cycle, and subsequently repeated prior to each cycle. Patients with WHO/ECOG performance status 0-2 were included for therapy. All patients had normal liver and bone marrow function with baseline GFR ≥ 50 mL/min/1.73 m^2. Two patients received 4 cycles of IA infusion of ^{177}Lu-DOTATATE at intervals of 8-12 weeks, one patient received 2 cycles IV followed by the 3rd and 4th cycles by IA route and the fourth patient had received only two cycles of IA infusion. In total, 12 cycles of IA infusions were administered (Table 1). Each patient received intramuscular administration of 30 mg long acting octreotide (LAR) on day 5 of each cycle of ^{177}Lu-DOTATATE therapy.

Procedure

Following premedication with intravenous ondansetron and dexamethasone administration, 7.4 GBq of ^{177}Lu-DOTATATE was administered IA through selective hepatic arterial catheterization, predominantly through femoral artery approach except on one occasion where the radial artery was catheterized. All patients, except for one received bilobar infusions (Refer to Table 1) by selective catheterization of the right and left hepatic arteries; maximum dose given to the lobe with large bulky disease volume. One patient received a single lobar infusion through selective catheterization of the right hepatic artery as there was a single large SSR avid lesion in the right lobe. All patients received amino acid infusion (Aminoven 10% with combination of amino acids having 25 gm of Arginine and 25 gm of Lysine in 2 liters of normal saline), beginning 1 hour before ^{177}Lu-DOTATATE administration and was continued for 4 to 6 hours after completion of the infusion for renal protection by reducing tubular reabsorption of

Patient	Age/Sex	Histopathology	Grade	Ki 67 index	History of surgery	Long acting octreotide/ Chemotherapy/ Previous liver directed therapy	Lu-^{177} DOTATATE Therapy No. of cycles / route of administration (IA / IV)	Single/ Bilobar infusion
Patient 1	61/Male	Well differentiated metastatic bronchial carcinoid	G-II	8-10%	Left lung lower lobectomy 6 years ago	Injection long acting octreotide at monthly intervals CAPTEM chemotherapy - 4 cycles with disease progression	4 cycles (2 cycles IV followed by 2 cycles IA)	Bilobar infusion 3rd and 4th cycle – Right lobe: 160 mCi, Left lobe : 30 mCi
Patient 2	55/Male	Well differentiated NET of pancreas Metastatic tumour deposits in liver nodules	G-II	6-8%	Distal pancreatectomy, splenectomy with two liver metastatectomy 6 years ago	90Y- TARE in right lobe of liver and bland ablation left lobe liver 2 years ago followed by injection long acting octreotide at monthly intervals with disease progression in left lobe of liver	4 cycles (IA)	Bilobar infusion 1st and 2nd cycle - Right lobe: 40 mCi, Left lobe: 160 mCi 3rd and 4th cycle - Right lobe: 20 mCi, Left lobe: 190 mCi
Patient 3	67/Male	Well differentiated NET of duodenum infiltrating peri duodenal fat	G-II	18-20%	Whipples Pancreaticoduodenectomy 2 years ago	Chemotherapy and Tab Everolimus - disease progression	4 cycles (IA)	Bilobar infusion 1st to 4th cycle - Right lobe: 140 mCi, Left lobe: 60 mCi
Patient 4	42/Male	Well differentiated NET of the pancreas with liver metastasis	G-II	5-6%	Inoperable disease Underwent CBD stenting 1 month ago	Nil	2 cycles (IA)	Single lobar infusion 1st and 2nd cycle- Right lobe: 200 mCi

Table 1: Clinical details of patients.

the radio peptide by the kidney. Optimal hydration with normal saline was maintained after ^{177}Lu-DOTATATE administration. Patients were isolated for 24 hours after ^{177}Lu-DOTATATE administration for observation and radiation safety purposes. A post therapy ^{177}Lu-DOTATATE whole body scan after each cycle was acquired to confirm the uptake of the radiotracer and for dosimetric purpose.

Follow up imaging

^{68}Ga-DOTANOC PET/CT whole body scan was done after 8 weeks of completion of the second and fourth cycles of ^{177}Lu-DOTATATE respectively and compared with baseline imaging to determine response to treatment. Complete blood counts including platelet counts were monitored on a weekly basis until they reached nadir levels. The clinical response, safety and toxicity profiles and tumor markers were assessed pre and post treatment, with a time frame of up to 3 months after last treatment. The objective tumour response evaluation was based on comparing the lesion size (RECIST 1.1 criteria) and intensity of tracer uptake of the liver lesions between the baseline and post therapy scans.

Results

Safety and Adverse effects

All patients tolerated the IA infusion of ^{177}Lu-DOTATATE therapy well, with none experiencing any significant procedure related acute side effects such as pain, bleeding, hematoma or infection at the femoral and radial puncture sites, pseudo aneurysms or contrast extravasation. The other complications associated with intra-arterial administration of the above therapy apart from the mentioned procedure related complications could be nausea, vomiting and worsening of liver function, with a scale of 1 for puncture site pain, 2 for nausea and vomiting and 5 for worsening of liver function. The immediate post treatment period was uneventful. While bone marrow cellularity was not assessed, the complete blood counts with platelets were monitored at serial intervals. Only one patient developed grade 1 hematological toxicity in the form of leucopenia and thrombocytopenia (less than 2 times the baseline values) after first cycle of PRRT and grade 2 toxicity after the second cycle. His liver function tests were stable. Remaining other patients had their complete blood counts well within normal limits. None of the three developed severe grade 3 or 4 treatment related hematological toxicity (Table 2). One patient developed transient increase of hepatic enzymes, which was about 4 times the normal value, which normalized subsequently. The alkaline phosphatase and Gamma glutamyl transpeptidase levels remained persistently elevated. No significant reductions in serum total bilirubin levels were seen in any of the patients. No significant change in the blood parameters noted after completion of the 4th cycle. No compromise in the quality of life of any patient was recorded. Infact, one patient had definite improvement in his quality of life compared to his baseline performance status. None of the patients developed acute radiation induced liver disease (RILD) or renal toxicity.

Tracer uptake by the lesions

The liver lesions demonstrated good ^{177}Lu-DOTATATE uptake in all the patients in the post therapy scans (Figure 1a-d).

Treatment response

Patient 1 : Post-operative case of bronchial carcinoid with SSR avid left hilar lesion and multiple other SSR avid pleural nodules, mediastinal lymph nodes, hepatic lesions and sclerotic bone metastasis. The SSR avid bulky liver lesions remained stable after 2 cycles of IV PRRT (Figure 2a and b). However, few of the extra hepatic sites of disease, predominantly the skeletal lesions showed good response (Figures 2-7). Post 3rd and 4th IA cycles, the liver lesions decreased by 7.94% as per RECIST 1.1 criteria indicating stable disease (Figures 2a-c, 3a-c and 4a-c). There was no significant fall in the SUVmax. The SSR avid residual soft tissue thickening in the left hilum, mediastinal nodal and pleural lesions were stable. The baseline PET CT showed both SSR avid and non-avid sclerotic skeletal metastases, few of the SSR avid bony lesions showing either decrease in the intensity of metabolic activity or resolution of tracer uptake (Figures 5-8) suggestive of partial response. While few lesions showed resolution of tracer uptake after 2 cycles of IV PRRT with interval sclerotic changes, others showed stable uptake after the 4th cycle following an initial mild decrease after 2 cycles of IV PRRT or mild tracer reduction after 2 cycles of IA PRRT. No new lesions were identified. The pleural, hilar lesion, mediastinal nodal and few other bone lesions were stable after 4 cycles of PRRT.

Patient 2: Case of primary NET of pancreas with liver metastases, underwent distal pancreatectomy, splenectomy with two liver metastatectomy 6 years ago. Baseline ^{68}Ga-DOTANOC PET CT showed multiple SSR avid hepatic metastases in both lobes predominantly in the left lobe, with a focal SSR avid extra hepatic soft tissue deposit in the left rectovesical pouch (Figures 9-11). Post 2 cycles of IA infusion of PRRT, there was significant reduction in size (30% decrease) and intensity of tracer uptake in the liver lesions with further decrease in size and metabolic activity after 4 cycles (69% decrease in size of liver lesions as per RECIST 1.1 criteria) suggestive of partial response (Figures 9b, c and 10b, c). Definite resolution of one of the liver lesions in segment IVb noted after 4th cycle with metabolic inactivity suggesting complete metabolic resolution (Figure 10c). The lesion measured 1.9 × 1.7 cm with SUVmax: 17.95 which decreased to 1.2 × 1.0 cm with SUVmax: 7.74 after the 2nd cycle and subsequently resolved after 4 cycles. The pelvic deposit remained stable with 18% decrease in size (Figure 11a-c).

Patient 3: NET of duodenum infiltrating periduodenal fat underwent whipples pancreaticoduodenectomy 2 years ago followed by chemotherapy with disease progression. He had multiple bulky SSR avid hepatic metastasis, with mesenteric deposit adjacent to the celiac axis. He also had low grade SSR avid opacities in the right lung with mediastinal lymphadenopathy. Post 2nd cycle of IA infusion PRRT, ^{68}Ga-DOTANOC PET CT showed significant decrease in the size of most of the liver lesions with interval necrosis (Figure 12a-f). Largest lesion in the right lobe (segment V/ VIII) measured 10.9 × 10.3 cm with SUVmax: 73, which decreased to 4.7 × 5.5 with SUVmax: 31 after 2nd cycle and further to 4.0 × 4.2 cm with SUVmax: 25 after the 4th cycle (Figure 13a-c). Liver lesions showed a 46% decrease in size after 2 cycles of and 58% decrease in size after 4 cycles of IA infusion PRRT suggestive of partial response. Corresponding decrease in SUVmax were also noted with fall in the SUVmax by 68.35% and 37.6% respectively in the largest liver lesions suggestive of partial metabolic response (Figure 12d-f). The mesenteric node and pleural/lung nodules remained stable, although resolution of few sub pleural nodules was noted.

Patient 4: Known primary NET of pancreas with liver metastasis, had SSR positive primary growth in the head and uncinate process of pancreas with liver metastasis in segment VI of the right lobe (14a and 15a, b). The primary showed mild decrease in the size of the lesion (5.5 × 6.4 × 6.3 cm to 5.1 × 4.5 × 6 cm) with significant fall in the SUVmax (71 to 32.5) after 2 cycles of PRRT. According to RECIST 1.1 criteria, there was decrease in size of the pancreatic lesion by 8.47% suggestive

Patients	Liver Function tests					Complete blood counts				
	Parameters	Baseline	After 2nd cycle	After 4th cycle	Follow up	Parameters	Baseline	After 2nd cycle	After 4th cycle	Follow up
Patient 1					After 1 year					After 1 year
	Total Protein (6.6-8.3 gm/dl)	6.1	6.1	6.2	6.4	Hemoglobin (g/dl)	11.5	11.1	12.2	13.8
	Serum Total Bilirubin (0.0-2.0 mg/dl)	0.69	0.79	0.95	0.51	Total WBC (4000-11000 cells/ mm^3);	4940	19291	6160	3710
	Alanine transaminase (ALT) 0-49 U/L	57	74	233	95	RBC count : (4.5-5.5);	3.8	4	4	4
	Aspartate transaminase (AST) 0-46 U/L	23	23	267	88	Platelet: (150000-450000)	191000	200000	127000	128000
	Alkaline phosphatase (ALP) 38-128 U/L	243	318	276	462					
	Gamma-glutamyl transpeptidase (GGT) 15 – 73 U/L	450	485	626	698					
Patient 2	Total Protein (6.6-8.3 gm/dl)	7.5	8.2	7.9	-	Haemoglobin (g/dl)	17	17.2	14.4	-
	Serum Total Bilirubin (0.0- 2.0 mg/dl)	1.34	1.42	1.35	-	Total WBC (4000-11000 cells/ mm^3);	14180	112100	10040	-
	Alanine transaminase (ALT) 0-49 U/L	27	74	35	-	RBC count : (4.5-5.5);	5.7	5.5	4.2	-
	Aspartate transaminase (AST) 0-46 U/L	27	52	36	-	Platelet: (150000-450000)	250000	201000	76000	-
	Alkaline phosphatase (ALP) 38 -128 U/L	74	90	91	-					
	Gamma-glutamyl transpeptidase (GGT) 15-73 U/L	43	485	72	-					
Patient 3					After 6 months					After 6 months
	Total Protein (6.6-8.3 gm/dl)	7	8.5	7.4	7.06	Hemoglobin (g/dl)	11.5	11.1	10.8	11.2
	Serum Total Bilirubin (0.0 – 2.0 mg/dl)	0.58	0.47	0.44	0.43	Total WBC (4000-11000 cells/ mm^3);	7400	7800	6400	7500
	Alanine transaminase (ALT) 0-49 U/L	31	13	14	18	RBC count : (4.5-5.5);		4	3.86	3.9
	Aspartate transaminase (AST) 0-46 U/L	36	23	23	29	Platelet: (150000-450000)	4.12	488000	449000	436000
	Alkaline phosphatase (ALP) 38-128 U/L	155	167	170	162					
	Gamma-glutamyl transpeptidase (GGT) 15-73 U/L	137	160	82	68					
Patient 4	Total Protein (6.6-8.3 gm/dl)	7.2	6.9	-	-	Hemoglobin (g/dl)	12.4	12.7	11.1	-
	Serum Total Bilirubin (0.0-2.0 mg/dl)	0.69	1	-	-	Total WBC (4000-11000 cells/ mm^3);	4690	3730	2722	-
	Alanine transaminase (ALT) 0-49 U/L	12.8	19.3	-	-	RBC count : (4.5-5.5);	4.34	4.37	3.8	-
	Aspartate transaminase (AST) 0-46 U/L	19.5	16.5	-	-	Platelet: (150000-450000)	130000	89000	75000	-
	Alkaline phosphatase (ALP) 38-128 U/L	118.9	124.6	-	-					
	Gamma-glutamyl transpeptidase (GGT) 15-73 U/L	56.1	55	-	-					

Table 2: Baseline and Post 177Lu – DOTATATE therapy liver function test and complete blood counts.

of stable disease (Figure 14). The segment VI liver lesion showed decrease in the size of the lesion by 9.09% suggestive of stable disease (Figure 15a-d). Amongst the four patients, two patients showed partial response to therapy according to RECIST 1.1 criteria and two patients showed stable disease. None of them had disease progression. All 4 patients reported significant improvement in symptoms and sense of well-being after treatment initiation. The quality of life had improved in one patient. In the others quality of life was maintained with no deterioration. All patients remained symptom free.

Biochemical response

Concordant decrease in serum chromogranin A levels were seen in three patients. Although there was a rise in the serum chromogranin A in one patient, he showed good partial radiological response, was asymptomatic, clinically well with no deterioration in his performance status (Table 3).

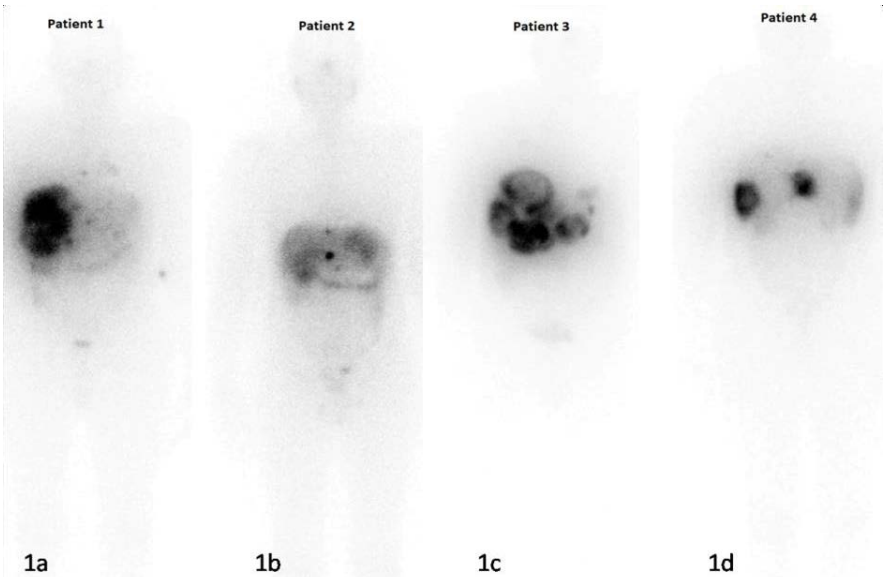

Figure 1: Post 177Lu- DOTATATE therapy scans show good 177Lu-DOTATATE uptake in the liver lesions in all four treated patients.

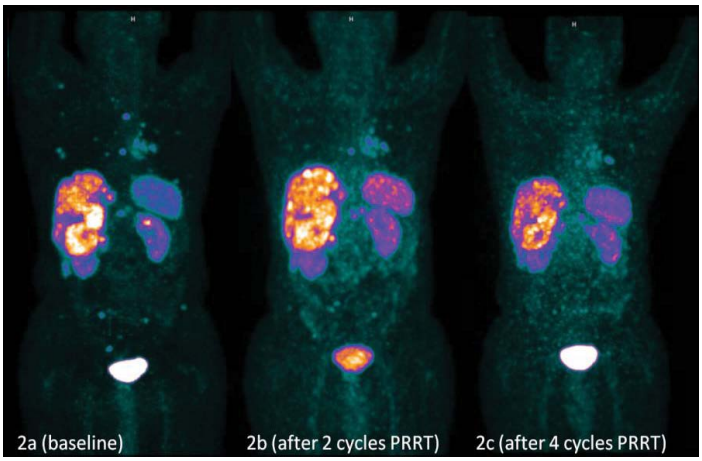

Figure 2: In Patient 1, the SSR avid bulky liver lesions remained stable after 2 cycles of IV PRRT (2b). Post 3rd and 4th IA cycles (2c), the uptake in few of the liver lesions decreased, with slight decrease in size. Most of the extra hepatic sites of disease showed regression after 2 cycles of IV PRRT, which improved further after next 2 cycles of IA PRRT.

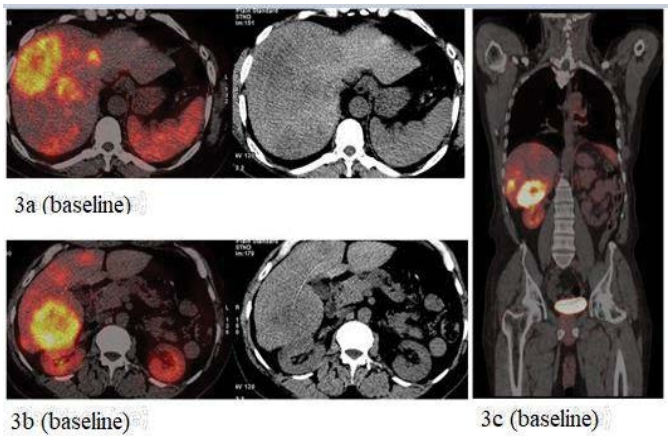

Figure 3: In patient 1, Liver lesions at baseline and after completion of 4 cycles of PRRT.

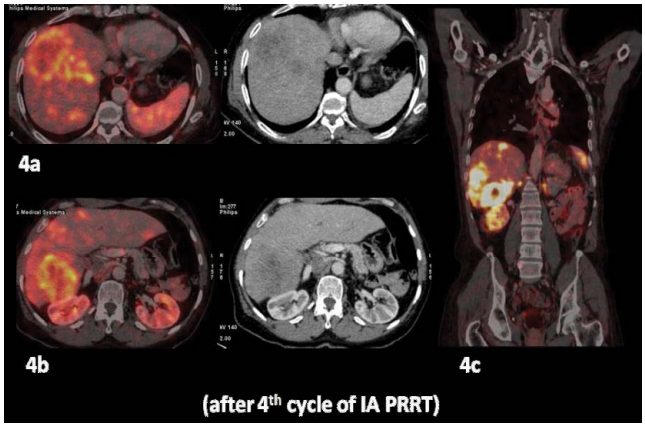

Figure 4: In patient 1, Liver lesions at baseline and after completion of 4 cycles of PRRT.

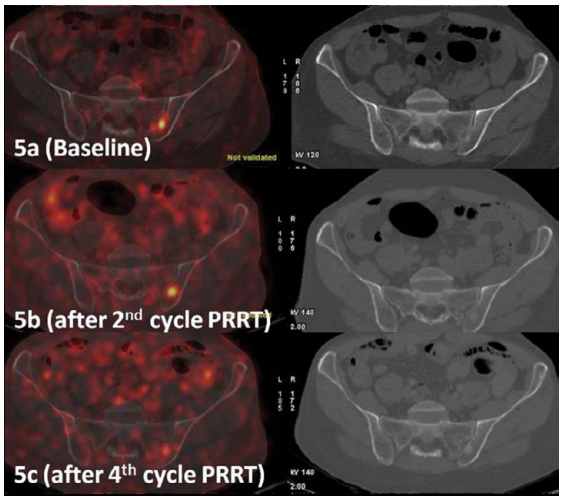

Figure 5: In patient 1, baseline PET CT showed both SSR avid and non-avid sclerotic skeletal metastases, few of the SSR avid bony lesions showing either decrease in the intensity of metabolic activity or resolution of tracer uptake suggestive of partial response. While few lesions showed resolution of tracer uptake after 2 cycles of IV PRRT with interval sclerotic changes, others showed stable uptake after the 4th cycle following an initial mild decrease after 2 cycles of IV PRRT or mild tracer reduction after 2 cycles of IA PRRT.

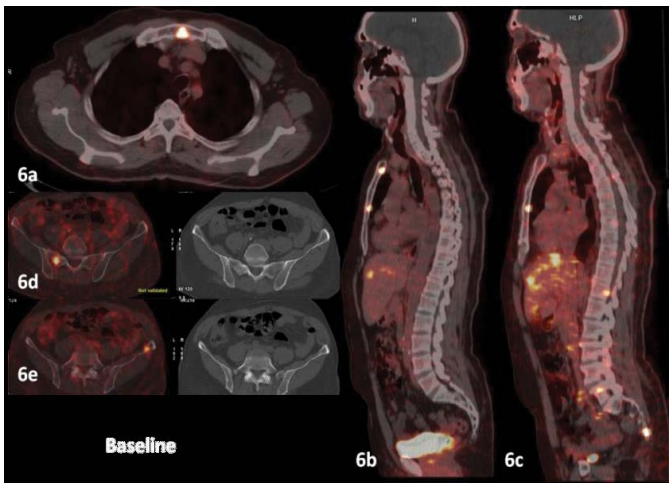

Figure 6: In patient 1, baseline PET CT showed both SSR avid and non-avid sclerotic skeletal metastases, few of the SSR avid bony lesions showing either decrease in the intensity of metabolic activity or resolution of tracer uptake suggestive of partial response. While few lesions showed resolution of tracer uptake after 2 cycles of IV PRRT with interval sclerotic changes, others showed stable uptake after the 4th cycle following an initial mild decrease after 2 cycles of IV PRRT or mild tracer reduction after 2 cycles of IA PRRT.

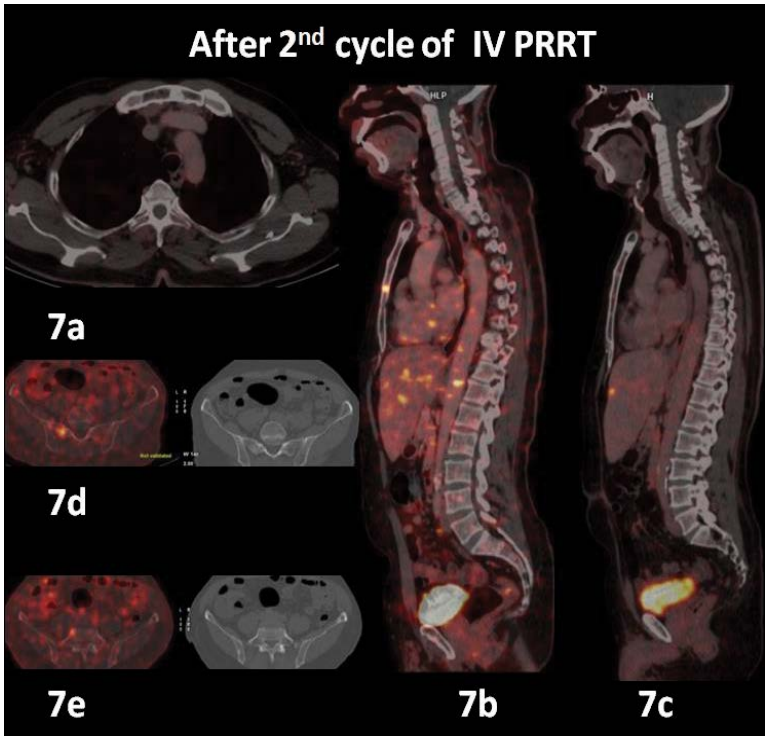

Figure 7: In patient 1, baseline PET CT showed both SSR avid and non-avid sclerotic skeletal metastases, few of the SSR avid bony lesions showing either decrease in the intensity of metabolic activity or resolution of tracer uptake suggestive of partial response. While few lesions showed resolution of tracer uptake after 2 cycles of IV PRRT with interval sclerotic changes, others showed stable uptake after the 4th cycle following an initial mild decrease after 2 cycles of IV PRRT or mild tracer reduction after 2 cycles of IA PRRT.

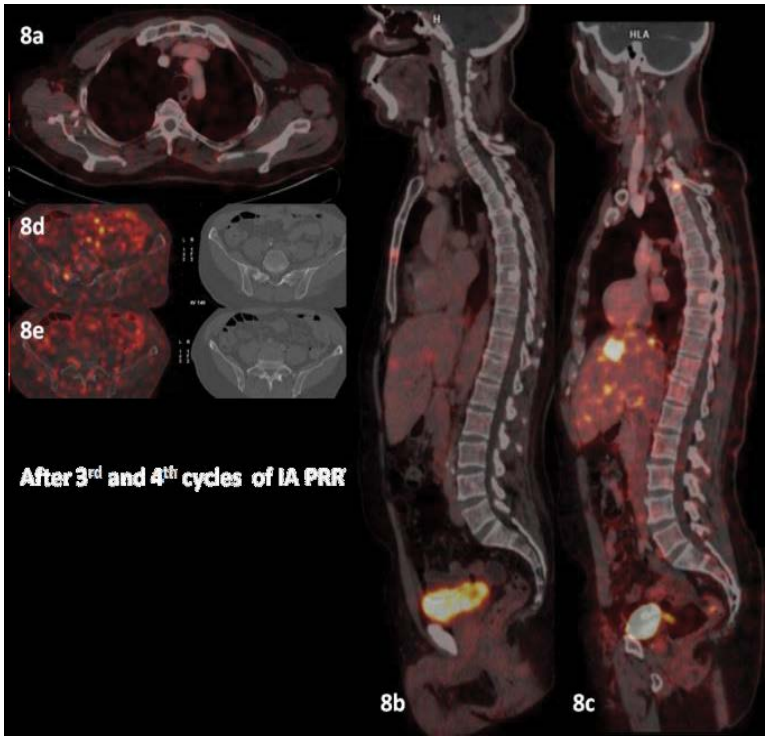

Figure 8: In patient 1, baseline PET CT showed both SSR avid and non-avid sclerotic skeletal metastases, few of the SSR avid bony lesions showing either decrease in the intensity of metabolic activity or resolution of tracer uptake suggestive of partial response. While few lesions showed resolution of tracer uptake after 2 cycles of IV PRRT with interval sclerotic changes, others showed stable uptake after the 4th cycle following an initial mild decrease after 2 cycles of IV PRRT or mild tracer reduction after 2 cycles of IA PRRT.

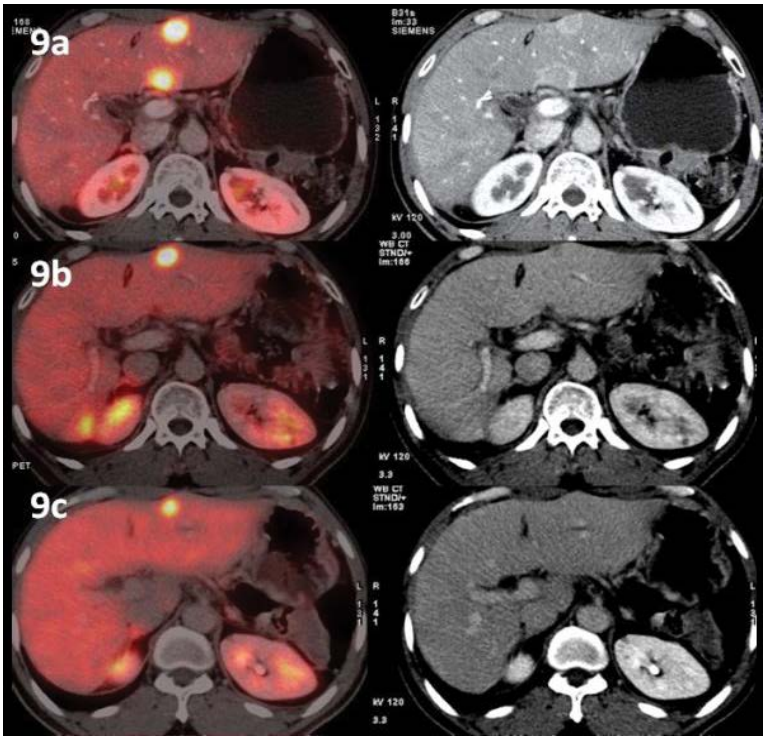

Figure 9: Patient 2- Baseline 68Ga-DOTANOC PET CT showed multiple SSR avid hepatic metastasis in both lobes predominantly in the left lobe, with a focal SSR avid extrahepatic soft tissue deposit in the left rectovesical pouch. b) Post 2 cycles of IA infusion of PRRT, there was significant reduction in size and intensity of tracer uptake in the liver lesions with further decrease in size and metabolic activity after 4 cycles (Figure 10b) suggestive of partial response.

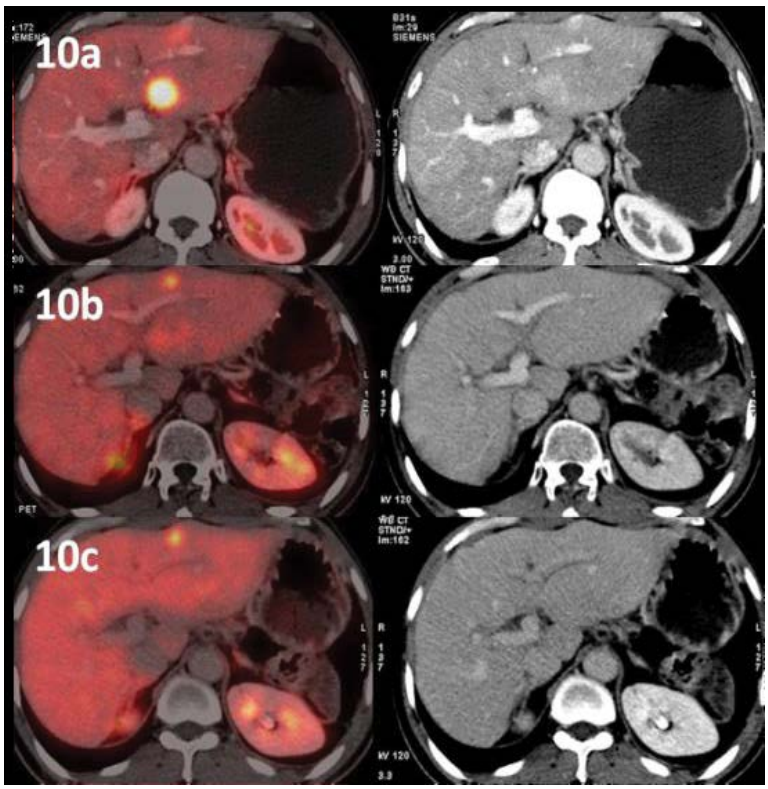

Figure 10: Definite resolution of one of the liver lesions in segment IVb noted after 4th cycle with metabolic inactivity suggesting complete metabolic resolution.

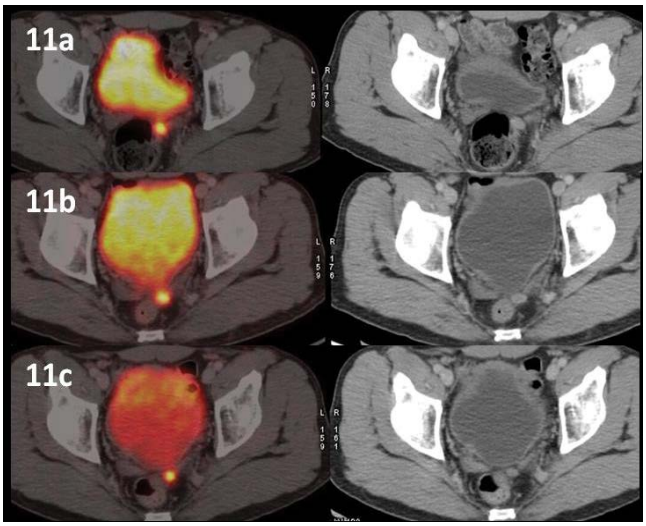

Figure 11: The pelvic deposit remained stable with no interval change.

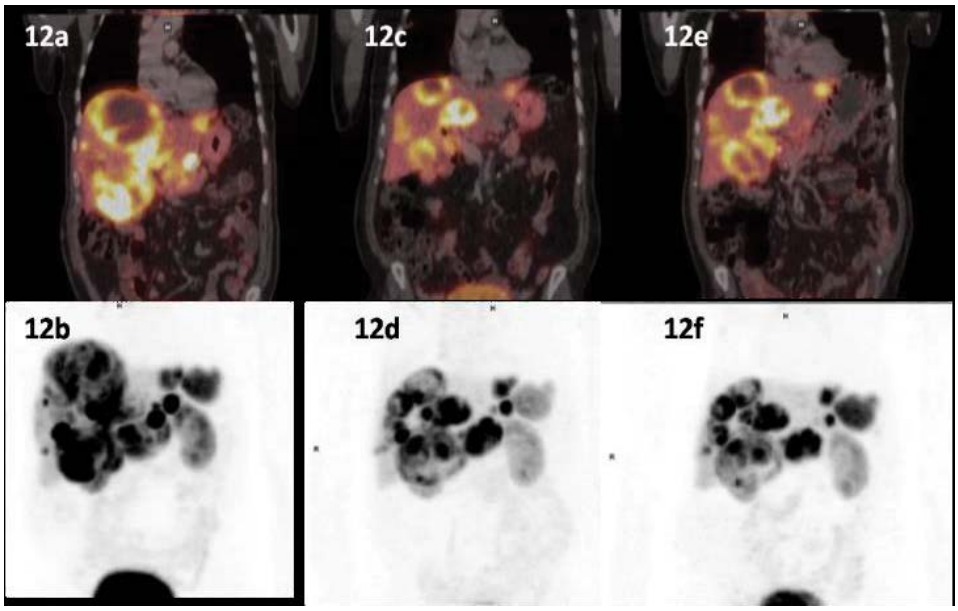

Figure 12: a & d) Patient 3 had multiple bulky SSR avid hepatic metastasis, with few extrahepatic sites of low grade SSR avid disease in the mesentery, right lung and mediastinum. **b & e)** Patient 3 Post 2nd cycles of IA infusion PRRT, 68Ga-DOTANOC PET CT showed significant decrease in the size of most of the liver lesions with interval necrosis. **c & f)** Patient 3 Further decrease in size of the liver lesions with decrease in metabolic activity seen after 4 cycles of IA infusion PRRT suggestive of partial response.

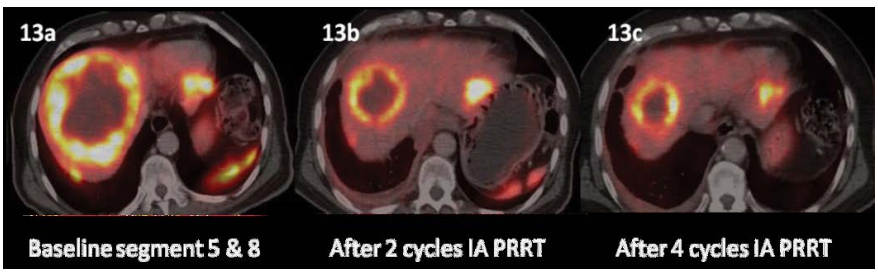

Figure 13: Patient 3. Largest lesion in the right lobe (segment V/ VIII) measured 10.9 x 10.3 cm with SUVmax: 73, which decreased to 4.7 x 5.5 with SUVmax: 31 after 2nd cycle and further to 4.0 x 4.2 cm with SUVmax: 25 after the 4th cycle with corresponding decrease in SUVmax suggestive of partial metabolic response.

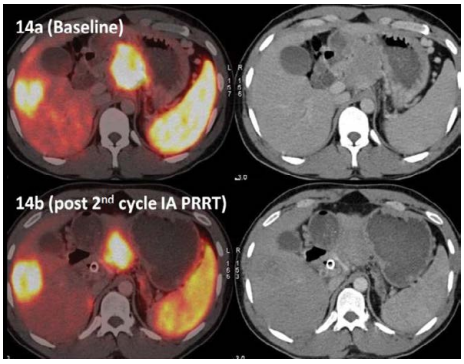

Figure 14: Patient 4, known primary NET of pancreas with liver metastasis, had SSR positive primary growth in the head and uncinate process of pancreas with liver metastasis in segment VI of liver showed mild decrease in the size of the pancreatic lesion with significant fall in the SUVmax (71 to 32.5) after 2 cycles of PRRT.

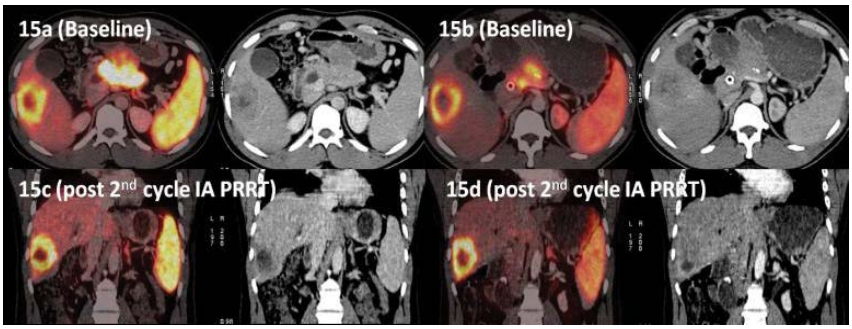

Figure 15: Patient 4, segment VI liver lesion remained stable after 2 cycles of PRRT.

Patients	Serum Chromogranin		^{68}Ga- DOTANOC PET CT (Liver mets alone/ with other mets)		Quality of life	Radiological response
	Pretreatment (baseline)	Post treatment (after 4 cycles of PRRT)	Baseline	Post treatment		
Patient 1	22020 ng/ml	7957 ng/ml	Left hilar lesion with multiple Multiple Ga-68 avid pleural nodules, mediastinal nodes, hepatic lesions and sclerotic bone metastasis.	Mild interval reduction in size and dota uptake of the liver metastasis with stable pleural, hilar, nodal and bones lesions.	Good at the end of 1 year	Stable
	After 2 cycles: 17620 ng/ml	Follow up at 1 year: 320.1 ng/ml				
Patient 2	26.95 ng/ml	41.9 ng/ml	Multiple Ga-68 Dota avid hepatic metastasis in both lobes (L>R) with focal DOTA avid deposit in the left rectovesical pouch.	Reduction in size and DOTA uptake of all the liver lesions with interval resolution of one of the previously seen lesions in segment IVB measuring 19 x 17 mm. Reduction in size and DOTA uptake in the pelvic deposit.	Good	Good Partial Response
Patient 3	3310 ng/ml	1018 ng/ml	Multiple Ga-68 avid hepatic metastasis. Mesenteric deposit adjacent to the celiac axis.	Reduction in size of most of the hepatic lesions with interval necrosis, largest lesion in the right lobe measuring 4.6 x 4.6 cm *vs* previous size of 11.2 x 9.9 cm. Reduction of few sub pleural nodules in the lungs with appearance of few lung nodules. Stable mediastinal nodes.	Good	Partial Response of liver lesions
	After 2 cycles:138 ng/ml	Follow up at 6 months: 312 ng/ml	Low grade Ga-68 avid right lung lesions with mediastinal lymphadenopathy.		Good	
Patient 4	5708 ng/mL	312 ng/ml	Ga-68 avid hepatic metastasis in the right lobe with primary in the head/ uncinated process of pancreas.	Reduction in size in the primary lesion in the head of pancreas with stable liver metastasis.	Good	Partial response in the pancreatic lesion with stable liver lesion

Table 3: Biochemical and Radiological response.

Discussion

The rationale for the use of PRRT is high expression of SSRs in NET cells, which involves internalization of the radio-labeled SSR analog complex. In the last few years, PRRT has emerged as a promising treatment with increasing evidence of efficacy on locally advanced or metastatic low-grade NETs (grades I or II) with positive expression of SSR type 2 [5-10]. The best objective responses have been reported in GEPNETs with partial responses ranging from 9% to 29% and complete remission from 2% to 6% [7,8]. Recently, Strosberg et al. [11] reported similar results from the NETTER-1 trial, the first phase-III multicentric randomized controlled trial evaluating 177Lu-DOTA0-Tyr3-Octreotate (Lutathera) in patients with inoperable midgut NETs with SSR expression in a patient population with limited therapeutic options for control of progressive disease. The study showed a statistically significant increase in progression free survival (65.2% vs 10.8%) and an objective response rate (18% vs 3%) in patients treated with Lutathera plus best supportive care as compared to 60 mg octreotide LAR at 20 months. In addition, the safety profile was proved acceptable with severe (grade 3 or 4) neutropenia, thrombocytopenia, and lymphopenia occurring in 1%, 2%, and 9%, respectively [11]. Recently 177Lu-DOTATATE therapy has received regulatory registration, with approval by the European Commission in September 2017 and by the US Food and Drug Administration (FDA) in January 2018. During an interim meeting in 2018, the NCCN panel included PRRT with 177Lu-DOTATATE as a treatment option for some advanced and/or metastatic gastrointestinal tract, bronchopulmonary, and thymic NETs (category 1 for midgut tumors) [18]. As liver metastases are often present in majority of metastatic NETs and represent a main prognostic factor, liver directed therapies have been explored, although there are no randomized or controlled trials comparing the locoregional treatments such as transarterial chemoembolisation (TACE), chemoembolization with drug eluting beads (TACE-DEB), transarterial embolisation (TAE), transarterial radioembolisation using 90Y microspheres (TARE), Radiofrequency ablation (RFA) and microwave ablation (MWA), including cytoreductive surgery. The basis for liver-directed treatments is that GEPNET metastases are usually highly vascular and are supplied by the hepatic artery while the normal liver parenchyma receives majority of its blood supply from the portal vein; hence have been recognized to be effective in symptom control, with a curative option of downsizing the tumor or making it amenable to systemic treatments in order to optimize the treatment effect on the remaining neoplastic tissue [19,20].

The standard route of administration of ^{177}Lu-DOTATATE is by systemic IV infusion. However, a substantial proportion of the dose is likely to be dissipated within the systemic circulation, with overall reduced dose reaching the target lesions. Since hepatic metastases depend mainly on the hepatic artery for their supply of oxygen and nutrients, the higher arterial radio peptide uptake during the first pass through the liver after IA administration is expected to result in superior tumor uptake, higher tumor absorbed radiation dose and subsequently better outcomes in patients with a high metastatic liver load. A preclinical rat liver metastasis model by Pool et al. [16] demonstrated ^{111}In-DTPA-octreotide tumor uptake to be twice as high after loco-regional administration *via* the hepatic artery and 1.06 to 9.2 fold increases in tumor-to-non tumor dose ratios than after IV administration [16,17]. Limouris et al. [14] showed encouraging results with IA infusion of PRRT with ^{111}In-DTPAOC, ^{90}Y-DOTATOC, and/or ^{177}Lu-DOTATATE [14]. It has been demonstrated that IA administration of the ^{68}Ga-DOTA(0)-d-Phe(1)-Tyr(3)-octreotide (DOTATOC) results in a high first-pass effect [13]. Recently, Kratochwil et al. [13] showed a mean 3.75-fold increase of ^{68}Ga-DOTATOC uptake at 40 minutes post injection after selective IA administration in GEPNETs [13,15]. The same group also reported on the pharmacokinetics after IA and IV infusion for 20 minutes of ^{111}In-DOTATOC in patients with GEPNETs, which showed a linear increase in the count rates within the tumour region of interest following IV infusion, which reached a maximum at 4 hours post injection. In contrast, IA infusion resulted in a 3.5- fold higher tumor uptake at the end of IA infusion compared with IV, with a subsequent washout, with tumor uptake reducing to a 2-fold ratio at 4 hours and a 1.3-fold ratio at 72 hours post injection [15]. Despite the washout effect, a higher tumor uptake at 4 hours and even 72 hours after IA infusion has been demonstrated, therefore mitigating the likelihood of decrease in the improvement of tumour uptake and predicting a relevant improvement in therapeutic tumour dose with ^{90}Y- or ^{177}Lu-labeled DOTATOC. The saturating curve following IA in contrast to IV infusion followed by an initial washout indicates that receptor saturation might be a limiting factor for selective IA PRRT [20]. In a pilot study, the therapeutic effectiveness of IA administered DOTATOC labeled with the therapeutic β emitters ^{90}Y and ^{177}Lu- DOTATOC into the hepatic artery of 15 patients with liver metastases arising from GEPNETs showed high rate of objective radiologic response which compares favorably with systemic chemotherapy and IV radio peptide therapy [7-11]. It has been previously observed that tumor uptake of DOTATOC is influenced by the total amount of administered peptide which depends on receptor occupancy [20], i.e. the maximum achievable tumor uptake might be limited by receptor saturation when the agent is delivered directly into the arterial supply of the tumor. Hence, use of high specific activity is pivotal along with optimization of the maximum concentration of peptide in the radiolabelled product per treatment cycle.

In this study, all patients tolerated the IA infusion of ^{177}Lu-DOTATATE therapy well. None of them experienced any significant acute side effects including radiation induced liver disease considering that the radio peptide was administered directly into the hepatic artery supplying the liver lesions. Only one patient developed transient increase of hepatic enzymes, which normalized subsequently. His serum bilirubin remained within normal limits. The alkaline phosphatase and Gamma glutamyl transpeptidase levels remained persistently elevated. He was clinically well at the end of one year following the last cycle of PRRT, with stable disease on post therapy ^{68}Ga-DOTANOC PET-CT and well preserved performance status. Only one patient developed up to grade 2 hematological toxicity after 2 cycles of PRRT. Remaining others had their complete blood counts well within normal limits. None of the patients developed grade 3 or 4 treatment related hematological toxicity.

None of the patients developed renal toxicity. During first pass circulation of the IA infusion, the radiolabelled ligand bypasses the renal circulation. As some amount of the radio peptide is partly trapped within the tumor, relatively fewer amounts reach the systemic circulation thereby minimizing the renal toxicity and radiation exposure to the kidneys [13]. No compromise was seen in the quality of life of any patient, with one patient demonstrating definite improvement in his quality of life as compared to his baseline performance index.

Though the sample size of our study was too small, therapeutic response was seen as partial response in two patients and stable disease in the other two, with none developing disease progression. The liver lesions demonstrated good ^{177}Lu-DOTATATE uptake in all the patients in the post therapy scans. The tumor uptake of the radio peptide depends on the tumor mass; tumor perfusion and the density of SSR type 2 receptors. After the initial uptake by the liver lesions,

a significant proportion of the radiopharmaceutical recirculates and enters the systemic circulation by second pass IV route to reach the other extra hepatic sites of tumors as seen in three patients with extra hepatic disease (Figures 2 and 5-11). The extra hepatic lesions showed sufficient uptake of ^{177}Lu- DOTATATE. Significant radio peptide uptake was also seen in the primary pancreatic growth in the fourth patient *via* the second pass IV circulation. Hence the IA infusion increases the therapeutic potential of liver lesions, without compromising treatment of the extra hepatic sites of disease.

There are obvious limitations in this study, mostly owing to the very small sample size and retrospective nature of study. Although all patients showed good therapeutic effect of the IA infusion of the radiolabelled peptide treatment, no head to head comparison with IV infusion was done, except in one patient, where the first two cycles were of intravenous infusion of PRRT followed by the 3rd and 4th cycles as intra-arterial. Though the target liver lesions decreased by 7.94% as per RECIST 1.1 criteria after 2 cycles of intra-arterial infusion in comparison to the intravenous infusion, it indicated stable disease. No significant difference was seen in the tracer uptake. While few skeletal lesions showed resolution of tracer uptake after 2 cycles of IV PRRT with interval sclerotic changes, others showed stable uptake after the 4th cycle following an initial mild decrease after 2 cycles of IV PRRT or mild tracer reduction after 2 cycles of IA infusion of PRRT. Therefore, there is limited evidence on the incremental tumor-to-non-tumor dose ratios in comparison to IV infusion. Hematological and nephrotoxicity are well known adverse events of PRRT and our study could possibly underestimate the real extent in view of the small sample size and needs validation by including larger number of patients. The initial results of the therapeutic efficacy of the IA infusion of PRRT is encouraging in this limited number of patients, however, this needs to be further validated in larger number of patients with longer follow up period. Lastly, this is only a feasibility study and does not address the overall survival benefits following IA infusions.

Conclusion

Our initial experience of IA administration of ^{177}Lu-DOTATATE therapy in patients with liver dominant metastases is promising, feasible, safe and tolerable. The preliminary therapeutic potential of this therapy appears encouraging; however, further prospective studies are needed to evaluate its impact on improving clinical outcomes and overall survival benefits. While only selected patients are eligible for IA administration of PRRT, this group of patients with predominant liver metastases could greatly benefit from this approach.

Source of Support

None

Conflicts of Interest

The authors declare they have no conflicts of interest and nothing to disclose.

Statement Regarding Contribution of Authors

The manuscript has been read and approved by all the authors, the requirements for authorship have been met and each author believes that the manuscript represents honest work.

Author Contributions

Conceived and Designed: Dr. S Sumati **Data analysis and Tabulation:** Dr. Arvind Rajan

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Patient Consent

Informed consents were obtained from all individual patients included in the study.

Ethical Approval

The procedures performed were in accordance with the ethical standards of the institutional ethics committee.

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