Clinics of Oncology

Research Article

ISSN: 2640-1037 |Volume 6

Survival Outcomes Associated With 177lu-Dotatate Therapy in Advanced Stage Gep-Net Patients: An 11-Year, Retrospective, Single Institution, Tertiary Care Experience

Yadav MP[1], Ballal S[1], Sahoo RK[2] and Bal C[1*]

[1]Department of Nuclear Medicine, All India Institute of Medical Sciences, India

[2]Department of Medical Oncology, Dr. B.R.A Institute-Rotary Cancer Hospital (IRCH), All India Institute of Medical Sciences, India

[*]Corresponding author:

Chandrasekhar Bal,
Department of Nuclear Medicine All India Institute of Medical Sciences, New Delhi 110029, India,
Tel No: +91-9013975659; Fax: 91-11-26588664.
E-mail: csbal@hotmail.com

Received: 05 Mar 2022
Accepted: 15 Mar 2022
Published: 21 Mar 2022
J Short Name: COO

Citation:

Bal C, Survival Outcomes Associated With 177lu-Dotatate Therapy in Advanced Stage Gep-Net Patients: An 11-Year, Retrospective, Single Institution, Tertiary Care Experience. Clin Onco. 2022; 6(3): 1-11

Keywords:

177Lu-DOTATATE therapy; GEP-NET patients; Survival; Prognostic factors

1. Abstract

1.1 Purpose: Peptide receptor radionuclide therapy in gastroenteropancreatic neuroendocrine tumors (GEP-NETs) has been used in the past two decades with a considerable prevalence of literature. However, due to the inherently indolent nature of GEP-NETs it is critical to evaluate the patients for a longer duration to assess the sustainability of treatment, survival patterns, and observe for late-side effects from treatment. The purpose of this study is to give an overview of an 11-year experience from a single centre on 177Lu-DOTATATE peptide receptor radionuclide therapy (177Lu-PRRT) in advanced stage GEP-NETs.

1.2 Patients & Methods: This retrospective analysis, with a median follow-up duration of 60 months (range: 6 – 172 months), included 226 patients treated with 177Lu-PRRT, (Males: 133; Females: 93; median age: 51 years [IQR: 42 – 60 years]). A total of 1097 cycles were administered, and all patients received at least 2 cycles of treatment. Over a median of five cycles (IQR: 3 – 6), the administered cumulative activity was 37 GBq. 116 patients received >37 GBq (22.2 – 44.4) of 177Lu-DOTATATE. The primary outcome endpoint in this study included the overall survival (OS). Secondary endpoints included the assessment of progression-free survival (PFS), morphological response as per RECIST 1.1 criteria (N=201), and the evaluation of the long-term safety profile as per the CTCAE version 5.0 criteria.

1.3 Results: The median OS was 72 months (95% CI: 55 - upper limit not attained) with five and 8-year survival probabilities of 56.9% and 42%, respectively. In multivariate analysis, the skeletal metastases [HR: 1.891; 95% CI: 1.176 to 3.041; P-0.0089], and disease progression on 177Lu-PRRT [HR: 2.287; 95% CI: 1.402 to 3.728; P-0.0010], had a significant impact on OS. The median PFS was 48 months (95% CI: 36 to 72 mo) with two and 4-year progression-free survival probabilities of 73.4% and 42.3%, respectively. Morphological response in 201 patients revealed complete response in 3%, partial response in 25.4%, stable disease in 45%, and progressive disease in 27% patients. Treatment-related toxicities were minimal.

1.4 Discussion: The long-term results reveal skeletal involvement and disease progression as the independent factors that predict the effectiveness and the survival of advanced stage GEP-NET patients treated with 177Lu-DOTATATE therapy.

2. Introduction

Neuroendocrine tumors (NETs) are indolent and hence unfortunately detected at an advanced stage of the disease where surgery is not an option. Somatostatin analogue (SSA) therapies, such as long-acting and short-acting octreotide, have proven beneficial in symptomatic and biochemical responses. However, achieving an objective response is under debate. The PROMID [1] and the CLARINET [2] trials investigated the anti-proliferative effect of octreotide and lanreotide in Grade I (GI) and GI/II GEP NETs, respectively. While both studies show a significant difference in the progression-free survival (PFS) between the SSA and the placebo groups [65.1% (95% CI, 54.0 to 74.1) vs 33.0% (95% CI, 23.0 to

43.3)], the overall survival (OS) between the groups were similar. This is apparent at a short follow-up duration in an indolent cancer like gastroenteropancreatic neuroendocrine tumors (GEP-NETs). The mTOR inhibitor, namely everolimus, is FDA approved for advanced pNET after the results of the RADIANT 3 trial, which reported an objective response rate (ORR) of 5%, disease control rate (DCR) of 78%, median progression-free survival (PFS) of 11.4 months and median OS of 44 months [3].

Following the SSA, 90Y-DOTATOC and 177Lu-DOTATATE peptide receptor radionuclide therapies (PRRT) have yielded promising results in well-differentiated GEP-NETs [4]. The most significant study on 177Lu-PRRT was the phase III randomized NETTER-1 trial, which compared the efficacy and safety of 177Lu-DOTATATE with high-dose long-acting octreotide (LAR) in patients with advanced midgut neuroendocrine tumors. However, the study was confined to midgut NETs with a short median follow-up duration of 14 months [5]. Extensive short-term efficacy studies are well established and have proven that 177Lu-DOTATATE has significantly induced symptomatic relief, ORR, and DCR in NETs [6, 7]. However, the data on the long-term efficacy of 177Lu-DOTATATE are limited and studied in a heterogeneous population of NETs [8-13]. Our previous publication demonstrated promising outcomes of 177Lu-DOTATATE therapy in terms of response, survival, and quality of life [9]. However, several patients were still undergoing treatment at that time, and the median follow-up duration was 32 months. Therefore, there is a need for a longer follow-up duration to get a better understanding on the long-term efficacy, survival and toxicity data of 177Lu-PRRT.

A few publications addressed long-term outcome results of 177Lu-PRRT; however, they included results of the overall role of 177Lu-PRRT in all types of NETs, irrespective of their origin [8-13] (Table 1). As GEP-NETs are the most prevalent type, there is a definite need for a long-term study to validate the short-term results of 177Lu-PRRT exclusively in GEP-NETs patients.

This study has been one of the first attempts to thoroughly examine the long-term outcome of these patients with an 11-year follow-up. We aim to report the long-term outcome of GEP-NET patients with an expanded cohort and assess the delayed toxicity profile. In a long-term follow-up cohort, the primary endpoint evaluated the OS and secondary endpoints, namely PFS, prognostic factors, and safety profile.

3. Materials and Methods

3.1 Patients

This single-institutional retrospective analysis was approved by the institute ethics committee of All India Institute of Medical Sciences, New Delhi, India, and patients were recruited between October 2010 to August 2021. The last date of follow-up assessment was 31st December 2021.

3.2 Eligibility Criteria

Inclusion criteria for PRRT were as follows: histological confirmation of NET Grade 1-3, positive 68Ga-DOTANOC PET/CT scan (Krenning score ≥3), at least one measurable target lesion on the 68Ga-DOTANOC PET/CT scan that was evaluable by RECIST criteria, prior history of anti-cancer treatments such as somatostatin analogues, radiotherapy, chemotherapy, and mTOR inhibitors. Exclusion criteria for PRRT were as follows: patients with baseline haemoglobin of less than 9 g/dL, platelet count of less than 60,000/μL, total leukocyte count of less than 3000/μL, serum creatinine of greater than 1.4 mg%, serum bilirubin of greater than 1.2 mg%, glomerular filtration rate (GFR) of less than 60 mL/min per 1.73 m2 BSA, Karnofsky Performance Status score of less than 30, Life expectancy <3 months and minimal or absent 68Ga-DOTANOC–positive scan were excluded from the study. All patients gave written informed consent to participate in the study.

3.3 Treatment Planning

Long-acting and short-acting somatostatin analogues were stopped four weeks and 72 hours, respectively, before 177Lu-DOTATATE therapy. Before every cycle of 177Lu-DOTATATE therapy, complete blood counts (CBC), kidney function tests (KFT), glomerular filtration rate (GFR), and liver function tests (LFT) were documented in all patients. Quality of life assessment parameters, including KPS and ECOG performance status, were assessed before every treatment cycle.

3.4 Dosing of 177Lu-DOTATATE+capecitabine

A median of 5.5 to 7.4 GBq 177Lu-DOTATATE was administered per cycle at time intervals of 8 to 12 weeks. Thirty minutes after administering pre-medications, amino acids were infused over 4 hours. After 30 minutes from the start of the amino acid infusion, 177Lu-DOTATATE was diluted in 50 mL of saline and co-infused over 30 minutes with a flow rate of 1·6 mL/min. An oral anti-cancer chemotherapeutic drug, namely capecitabine 1250 mg/m2 (Xeloda; Roche Products, South San Francisco, California), was prescribed as a radiosensitizer from day 0 to 14, commencing on the morning of 177Lu-DOTATATE therapy. The same protocol was repeated at subsequent PRRT cycles. Following each treatment, post-therapy 24-hour planar whole-body scans were performed using a dual-headed gamma camera (GE).

3.5 Follow-up

Follow-up of all patients was performed at 2, 4, and between 8 to12 weeks after each cycle of 177Lu-DOTATATE therapy with CBC, KFT, GFR, and LFT to assess the toxicity according to the National Cancer Institute for Common Toxicity Criteria version 5.0 [14]. The interval between consecutive therapy cycles of each patient was 12 to 16 weeks. 68Ga-DOTANOC PET/CT scans were obtained for restaging of disease at 7±1 weeks after every two to three cycles of 177Lu-DOTATATE therapy.

Patients on oral capecitabine were kept under keen observation for any adverse effects of the drug. During a median follow-up duration of 60 months (range 6 – 172 months), patients were administered 177Lu-DOTATATE therapy over 2 to 9 cycles with a median cumulative dose of 37 GBq. Treatment was discontinued in patients who completed 6 to 9 cycles of therapy with a maximum administered cumulative activity of 44.4 GBq (1200 mCi) (15) or developed progressive disease (PD) or dedifferentiation of tumor or achieved a complete response to treatment or denied to take further treatment.

The primary endpoint was OS. The key secondary endpoint was progression-free survival. The other secondary endpoints included ORR as per RECIST 1.1 criteria [16], clinical response, and adverse event profile. Primary events were considered as morphological disease progression or death, whichever occurred first.

3.6 Clinical Response

Clinical response, assessed with Karnofsky Performance Scale KPS [17], was evaluated before and after every treatment cycle. During the follow-up, documentation parameters included last contact, length of follow-up, check the alive/deceased status of the patient, date and details of events. When unavailable, mortality data were retrieved by phone calls to the patient's family. Treatment was discontinued if patients experienced disease progression, and further treatment options were started as per the discretion of the multi-modal treating team.

4. Definitions and Outcome Endpoints

4.1 Events

Primary events were considered as progression or recurrence of disease and/or development of ascites, pleural effusion, pericardial effusion, as per RECIST (version 1.1) [16], or death due to disease, whichever occurred first

4.2 Outcome Measures

4.2.1 Primary Outcome Measure

Overall Survival (OS)

Definition: Time from the initiation of 177Lu-DOTATATE PRRT to the occurrence of death due to any cause or the date of the last contact.

Patients with lost follow-up and not known to have died were censored at the date of the last contact.

4.2.2 Secondary Outcome Measures

4.2.2.1 Progression-free survival (PFS)

Definition: From the date of initiation of 177Lu-DOTATATE PRRT until the date of first observation of radiographic progression according to RECIST version 1.1 criteria or the development of pleural/pericardial effusion or ascites, or death due to any reason, whichever occurred first.

4.2.2.2 Objective response rates (ORR)

Definition: Complete or partial response in soft tissue, lymph node, or visceral lesions as per RECIST 1.1 criteria [16].

Imaging Modality: Diagnostic 68Ga-DOTANOC PET/CT

Time Frame: From the date of the first dose until the date of the first documented disease progression

First scan (Baseline scan): Conducted before the initiation of 177Lu-DOTATATE therapy.

Follow-up scans: Repeated after 7±1 weeks after completing every 2–3 cycles of 177Lu-DOTATATE or if the principal investigator suspects clinical disease progression or as per the PIs discretion.

After completing the 177Lu-DOTATATE therapy regimen, follow-up scans were performed at every 6-to-12-month intervals or if any signs of clinical disease progression are observed or up to the initiation of other anti-cancer treatments.

4.2.2.3 Clinical response: Clinical response assessment was done by the Karnofsky performance status (KPS). The KPS ranged from 100 to 0 (100: no evidence of disease and no complaints; 0: dead).

Time Frame

First-time point: Before the initiation of 177Lu-DOTATATE therapy

Second-time point: At eight weeks of each cycle of 177Lu-DOTATATE therapy, or study withdrawal, or death.

4.2.2.4 Adverse-event profile: Patients were given a diary to document any side effects or discomfort.

Treatment-related AEs were documented using National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) [14].

Time Frame: The distribution of adverse events (AE) was evaluated throughout the treatment and follow-up period by monitoring relevant clinical, laboratory, and imaging parameters. All AEs, including treatment-related or not, serious adverse events, deaths were recorded.

4.2.2.5 Disease Control Rate

Definition: Percentage of patients who have achieved a complete response, partial response, or stable disease according to RECIST 1.1 criteria.

Time Frame: From the date of first 177Lu-DOTATATE treatment until the date of first documentation of radiographic progression or the date of death due to any cause, whichever occurs earlier.

5. Statistical Analysis

D'Agostino-Pearson Test was used to analyze the distribution of the data. Quantitative data are summarized as means and standard deviations for normally distributed data. Data with skewed distribution are summarized as medians with Interquartile Ranges

(IQR). Kaplan-Meier survival curves were constructed to derive the overall and progression-free survivals. Log-rank test derived the P-value between the survival curves. Univariate and multivariate cox-proportional hazards models were used to identify the predictive factors associated with the OS and PFS. Differences between the two groups were considered significant if the P-value was <0.05. The data were analyzed using MedCalc Version 15.0.

6. Results

Baseline patient demographics are detailed in table 2. In 192 (85%) patients, WHO NET Grades were I/II, 18 (8%) had well-differentiated Grade III, and the tumor grade was unknown in 16 (7%) patients. The most common site of the primary tumor was the pancreas in 87 (38.5%), bowel in 94 (41.5%), and in 28 (12.6%) patients; the disease was confined to the abdomen, but the origin of the primary NET was unknown (Table 2).

Before PRRT, most patients received Sandostatin LAR (n=165, 73%), and 78 patients underwent surgery. Among the 28 who received chemotherapy, 15 received CAPTEM, and 13 received other chemotherapies such as cisplatin (n=4), carboplatin (n=4), gemcitabine (n=2), and sunitinib (n=5). Four patients received two lines of chemotherapies.

The SSTR expression on the 68Ga-DOTANOC PET scan was observed in 70.3% of the patients in the primary tumor site. The metastatic disease was documented in all, except one patient, and the liver was the most common site of metastasis 87%, followed by lymph nodes in 84% (Table 2). The mean duration from the diagnosis to the initiation of 177Lu-PRRT was 27.9 ± 25.1 months (range: 12 – 56). The median follow-up duration was 60 months (range: 6 - 172 months).

Table 1: Overview of published data on long-term outcome of 177Lu-PRRT in NETs

0	Type of NETs	Site of primary tumor	Number of patients (n)	Cumulative activity(GBq)	Median follow-up duration(months)	Morphological response (RECIST 1.1) (%)	DCR (%)	OS (months)	PFS (months)	Leukemia n (%)	MDS n (%)	Grade 3/4 toxicity (n)
Brabander et al. (2017) [8]	NETs	GEP NETs Bronchial carcinoids	610	443 received ≥22.2 GBq	78	PR: 39% SD: 43% PD:12%	82%	63 (95% CI 55-72)	29 (95% CI 26-33)	4 (0.7%) after 55 mo of first therapy	9(1.5%) after 28 months range 9-41 months after first therapy.	Platelets: 30/582 Total WBC count: 32/582 Haemoglobin: 22/582 Total WBC count: 32/582 Haemoglobin: 22/582 Aminotransferases (aspartate transaminase and/or alanine transaminase): 20/581 Aminotransferases (aspartate transaminase and/or alanine transaminase): 20/581 Creatinine: 2/581
Ballal et al. (2017) [9]	NETs	Pancreatic NET: 49Foregut: 30Foregut: 30Midgut: 34Hindgut: 12Paraganglioma: 20 Liver: 5Unknown primary: 16Heart: 1	167	21.1 ± 9.7(range: 10 – 50 GBq)	Mean: 32.4	PR: 20.9% MR:7.5% SD: 55%PD:16%	84%	58 (95% CI,48–58)	46 (95% CI, 41–58)	0	0	0
*Kunikowska et al. (2017) [10]	NETs		59	11.1–16.65 GBq	75.8	CR: 2%,PR: 22%SD: 65% PD: 6%	89%	82	32.2	0	1	Nephrotoxicity: 1

Demirci et al.(2018) [11]	Grade3 NETs	Lung: 29 Pancreas: 68 Nonpancreatic GEP-NETs: 42 Pheochromocytoma – paraganglioma: 12 NET of unknown primary site: 27 Ovary: 5 Prostate: 1 Kidney: 1 Thymus: 1	186	mean: 5.04 GBqper cycle	30.6	CR: 3.1% PR: 46.9% PD: 28.1% SD: 21.9% (n = 75)	DCR: (WHO) GI: 74%, G2: 73% G3: 60%	mean: 55	36.4	0	0	Kidney toxicity: 2
*Baum et al. (2018) [12]	NETs	Bronchial: 75 Pancreas: 384 Small Intestine: 315 CUP: 151 Other: 123	1084	mean: 18.84 GBq (range: 1.4 GBq to 63.9 GBq)	-	-	-	51	19	22 patients (2.1%)	Leucocytes: 0.1% Thrombocytes: 0.1% Hemoglobin: 0.2% Chronic kidney disease: 0.3%	
Sitani et al. (2021) [13]	NETs	Pancreatic: 142 Small intestine: 112 Large intestine: 42 Stomach: 16 Gall bladder: 9 Kidney: 1 Lung/ mediastinum/thymus: 58 Unknown primary site: 88	468	30 GBq (12.76 GBq to 42.4GBq)	46	CR: 3% PR: 27% SD: 60% PD: 10%	90%	NR	NR	0	0	hematological toxicity: 1 patient grade 3, and grade 4 was found in 2 patients (0.4%) and 1 patient (0.2%) respectively.

*Tandem 90Y /177Lu-PRRT

GEP-NETs: gastroenetropancreatic neuroendocrine tumors; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease, MDS: Myelodysplastic syndrome.

Table 2: Baseline demographic profile of 226 patients

Variables	**Values**
Age in years (median; IQR)	51 [42 – 60]
Gender	
Male	133 (59%)
Female	93 (41%)
Prior treatments	
Previous Surgery	148 (65.4%)
Sandostatin	165 (73%)
Prior chemotherapy	28 (12.3%)
Everolimus	29 (13%)
Palliative radiotherapy	58 (25.6%)
Other	25 (11%)
Time duration from the time of diagnosis to initiation of PRRT (months)	
Median [range]	18 [12 -156]
Origin of NET	
Foregut	136 (60%)
Pancreas	87 (38.5%)
Stomach	15 (6.6%)
1st and 2nd parts of duodenum	34 (15%)
Midgut	34 (15%)
Appendix	2 (0.9%)
Mesentery	3 (1.3%)
Ileum	22 (9.7%)
3rd and 4th parts of duodenum	5 (2.2%)
Jejunum	2 (0.9%)
Hindgut	28 (12.3%)
Descending colon	5 (2.2%)
Rectum	21 (9.2%)
Caecum	2 (0.8%)
Abdominal NET with unknown primary	28(12.3%)
Tumor Grade	

Ki 67 Tumor Proliferation Index	
<2%	86 (38%)
3% - 20%	106 (47%)
>20%	18 (8%)
Not accessible	16 (7%)
Concomitant radiosensitizing agent (Capecitabine)	205 (91%)
Extent of Cancer on ^{68}Ga-DOTANOC PET/CT Scan	**Number (%)**
Primary	159 (70.3%)
Lymph node	190 (84 %)
Liver	196 (87 %)
Bone	65 (29 %)
Lungs	33 (14.6 %)
Other sites	39 (17%)
Median Number of ^{177}Lu-DOTATATE Cycles [IQR]	5 [3 – 6]
Median cumulative activity in GBq [IQR]	37 [22.2 – 43.66]
Median Follow-up Duration in Months (range)	60 months (range: 6 – 172 months)

6.1 177Lu-PRRT treatment Cycles

A total of 1097 cycles were administered, and all patients received at least 2 cycles of treatment. Over a median of five cycles (IQR: 3 – 6), the median administered cumulative activity was 37 GBq. 116 patients received >37 GBq (22.2 – 44.4) of 177Lu-DOTATATE.

6.2 Imaging Response

The baseline diagnostic 68Ga-DOTANOC PET/CT was performed in all patients; however, the RECIST 1.1 criteria could be assessed in 201 patients, 6 achieved complete response (3%), 51 had a partial response to treatment (25.4%), 90 had stable disease (45%) and disease progression was noted in 54 patients (27%). As a result, 177Lu-PRRT achieved an ORR of 28.4% DCR of 73.4%.

The treatment response according to the type of primary tumor is listed in table 3. Radiological disease progression was observed in 16.3% (14/86) of Grade 1, 31% (33/106), Grade 2, and 28% (5/18) of grade III NETs. Among those patients who achieved CR, 83.3% had WHO Grade I, and 16.7% had Grade II NET.

Table 3: Morphological response according the site of primary tumor

Site of primary tumor	**CR (N=6)**	**PR (N=51)**	**SD (N=90)**	**PD (N=54)**	**NOT ASSESSED (N=25)**
Pancreas (n=87)	2	17	35	25	8
Stomach (n=15)	2	3	5	5	0
Duodenum (n=39)	0	14	17	4	4
Appendix (n=2)	0	0	0	1	1
Mesentery (N=3)	0	1	1	1	0
Jejunum (n=2)	0	2	0	0	0
Ileum (n=22)	2	8	7	3	2
Colon (n=5)	0	1	3	1	0
Caecum (n=2)	0	1	1	0	0
Rectum (n=21)	0	3	4	10	4
Abdominal NET/unknown primary (n=28)	0	1	17	4	6

7. Survival analysis

7.1 OS, PFS, and Predictive Factors

Overall, 77 patients (34%) died during the follow-up. The median OS was 72 months (95% CI: 55 –NR) with five and 8-year survival probabilities of 56.9% and 42%, respectively (Figure 1a). On both univariate and multivariate analysis of bone metastases [HR: 1.8914; 95% CI: 1.1763 to 3.0413; P-0.0089] (Figure 1b), disease progression on 177Lu-PRRT [HR: 2.2872; 95% CI: 1.4029 to 3.7288; P-0.0010] (Figure 1c), were associated with significantly poorer OS (Table 4)

The PFS was 48 months (95% CI: 36 to 72 mo). The two and four -year progression-free survival probabilities were 73.4% and 42.3%, respectively (Figure 2a). On univariate analysis, only the presence of bone metastases was associated with a poor PFS (Figure 2b) (Table 5).

Table 4: Univariate and multivariate Cox-proportional hazard regression of factors associated with overall survival.

	Univariate Analysis			**Multivariate Analysis**	
Parameters	**Median OS (mo)**	**P-value (Log-rank)**	**HR; 95% CI**	**P-value (Log-rank)**	**HR; 95% CI**
Age (years)					
≤51	72	0.7479	0.9307 (0.5951 to 1.4556)		
>51	84				
Gender					
Male	84	0.9513	1.0139 (0.6459 to 1.5916)		
Female	72				

Skeletal metastases					
Yes	48	0.0013	2.0329 (1.2128 to 3.4076)	0.0089	1.8914 (1.1763 to 3.0413)
No	84				
Liver metastases					
Yes	72	0.5119	1.2574 (0.6639 to 2.3814)		
No	97				
Chemotherapy					
No	84	0.5558	0.7947 (0.3911 to 1.6146)		
Yes	67				
mTOR inhibitors (Everolimus)					
Yes	54	0.3309	1.2885 (0.7206 to 2.3037)		
No	84				
WHO tumor grade					
III	48	0.6187	1.2551 (0.4599 to 3.4251)		
I/II	62				
Previous surgery					
Yes	67	0.7094	0.9171 (0.5730 to 1.4676)		
No	84				
Previous sandostatin LAR					
Yes	72	0.2094	1.4372 (0.8532 to 2.4210)		
No	84				
Disease progression					
Yes	49	0.0001	2.4482	0.001	2.2872 (1.4029 to 3.7288)
No	Not attained		(1.5421 to 3.8867)		

OS: Overall survival; HR: Hazards ratio; 95% CI: 95% confidence interval

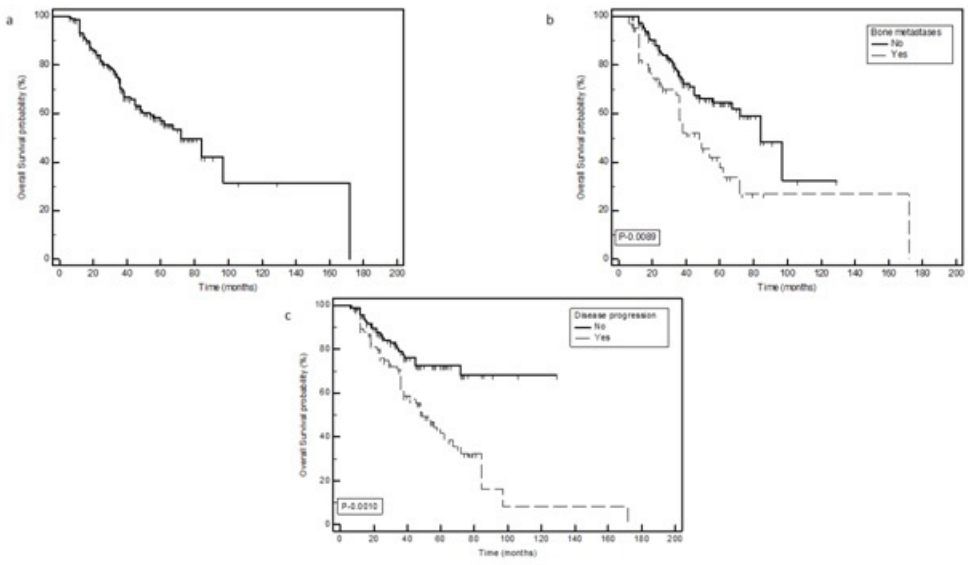

Figure 1: a. Overall Survival by stage, b. overall survival by bone metastases, c. Overall survival by disease progression.

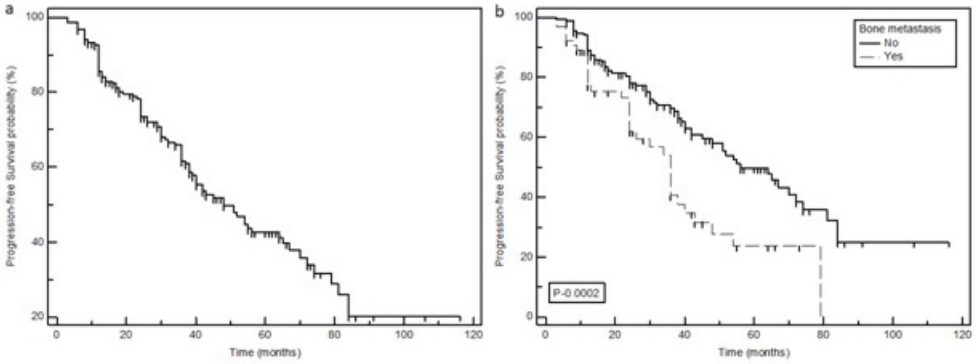

Figure 2. a. progression-free survival, b. PFS by bone metastases

Table 5: Univariate Cox-proportional hazard regression of factors associated with progression-free survival.

	Univariate Analysis		
Parameters	**Median PFS (mo)**	**P-value (Log-rank)**	**HR; 95% CI**
Age (years)			
≤51	45	0.8619	0.9665 (0.6529 to 1.4307)
>51	48		
Gender			
Male	45	0.6584	1.0924 (0.7345 to 1.6246)
Female	48		
Skeletal metastases			
Yes	34	0.0002	2.0742 (1.2930 to 3.3274)
No	72		
Liver metastases			
Yes	43	0.3386	1.333 (0.7744 to 2.2953)
No	67		
Chemotherapy			
No	48	0.8978	1.0381 (0.5749 to 1.8746)
Yes	43		
mTOR inhibitors (Everolimus)			
Yes	38	0.1689	1.4078 (0.8040 to 2.4651)
No	64		
WHO tumor grade			
III	26	0.3893	1.3405 (0.6165 to 2.9134)
I/II	48		
Previous surgery			
Yes	56	0.4207	1.1793 (0.7888 to 1.7631)
No	39		
Previous sandostatin LAR			
Yes	43	0.7135	1.0905 (0.6869 to 1.7310)
No	48		

PFS: Progression-free survival; HR: Hazards ratio; 95% CI: 95% confidence interval

7.2 Toxicity

Acute side effects included nausea in 18% after amino acid administrations, abdominal pain or discomfort in 8%, and vomiting in 5%. Nausea and vomiting commenced at amino acid infusion and mostly subsided within 48 hours. Abdominal pain or discomfort was usually encountered within the first day after the treatment and lasted for 2 to 3 days post-treatment.

Due to previous multi-line treatments and advanced disease status, out of 226 patients, 28 (12.4%) had G2 anaemia at the time of recruitment, and 82 (36.3%) had G1 anaemia. Two patients developed G3 anaemia; however, both had G2 anaemia at recruitment. Prior to commencing treatment, G2 leukopenia was observed in 7 patients and improved in all patients over the treatment period, but no G3/4 leukopenia events were documented. Before therapy, two patients had G1 thrombocytopenia; however, normalization of the platelet counts was observed during the course of therapy in both. No patient developed G4 haematological toxicity in the present series.

G2 bilirubin toxicity was reported in 10 patients at the baseline. However, no G3/4 bilirubin toxicity was reported. ALP G3 was noted at the baseline in 12, G2 in 16, and G1 in 58 patients. Among 12 patients with G3 elevated ALP values at the baseline, six showed a promising decrease to G1 after the initiation of 177Lu-PRRT and normalization of ALP values in two patients. However, four remained to have G3 throughout the treatment. At the time of recruitment, 22 patients had G1 elevated creatinine levels which normalized during the treatment period in 10 patients. The remaining 12 patients had persistent G1 toxicity, but no patient demonstrated deterioration in the kidney parameters. No case of kidney and hepatic failure was documented.

Myelodysplastic syndrome (MDS) occurred in two patients (0.8%) after a follow-up of 6 and 10 years after the initiation of 177Lu-DOTATATE therapy, and both patients died within two years of MDS diagnosis. Capecitabine therapy was discontinued

in 23 patients because of G2 nausea in 7 patients, hand-foot syndrome in 10 patients, and QTc prolongation in 6 patients.

8. Clinical Response

Out of 226 patients, CR was found in 55 patients (24.3%), PR in 88 patients (39%), SD in 33 patients (14.6%), whereas PD was found in 50 patients (22%). The pre-therapy median KPS score was 74, which improved to 85 following 177Lu-PRRT.

9. Discussion

In the last few years, a handful of retrospective studies have reported the long-term outcome of 177Lu-DOTATATE therapy in the treatment of NETs [8-13] (Table 1). All previous reports have demonstrated the overall efficacy of 177Lu-DOTATATE therapy in treating various kinds of NETs irrespective of the site of the primary tumor.

The NETTER-1 Phase III trial [5] compared the 177Lu-DOTATATE to high dose octreotide LAR therapy in patients with inoperable, progressive midgut NETs. In line with the treatment cohort of the NETTER group, our patient population included patients with GEP-NETs, and adopted fixed-dose protocols and treatment cycle intervals of 8-to-12 weeks. Hence comparing our long-term data results with the short-term consequences of the NETTER Phase III trial was ideal as it was essential to correctly interpret and accurately conduct a head-to-head comparison in a similar patient population and treatment setting. However, it should be noted that the NETTER -1 results were focused on short-term outcomes. Therefore, in a large series of patients, the long-term outcome of a prospective study on survival and prognostic factors is not outlined.

The results of our study on 177Lu-DOTATATE therapy in GEP NETs proved this therapy effective with a DCR of 73.4%. In addition, it improved the OS and PFS of patients by 72 and 48 months, respectively, which corroborates well with the NETTER trial results and the other long-term reports [5, 9, 11].

We found bone metastases and disease progression on 177Lu-PRRT were independent predictive factors for shorter OS. The OS was 48 months in patients with bone metastases versus 84 months in those without the involvement of the bone. In addition, a retrospective single-institutional study on 341 patients with well-to-moderately differentiated NETs who underwent various anti-cancer treatments revealed patients with skeletal metastases had shorter survival (median, 52 months) compared to the control group (median, 98 months; P = 0.024) (18).

Our results are similar to reports by Abou Jokh et al. [19] and Swiha et al. [20], who demonstrated that the presence of bone metastases was associated with shorter OS of 27.8% and 48.9%, respectively in patients with well-differentiated NETs who received 177Lu-PRRT. Swiha et al. [20] identified bone deposits greater than 5 as an independent predictor of shorter OS (35.3 mo). Similarly, Demerci et al. [11] observed the OS was affected in patients with bone metastases.

The prognostic impact of the type of distant metastases varies among the published series where the current study and Demerici et al. [11] do not find a correlation between the presence of liver metastases and survival. On the other hand, Kwekkeboom et al. [21] demonstrated a significantly reduced survival in patients with liver metastases. The presence of distant metastases has been sustained to be one of the most prominent factors among a series of studies [9, 11, 18-21].

Disease progression was observed in 27% of the patients, which was similar to the rates reported by Demirci et al. [11] according to the RECIST criteria. However, unlike our observations, the disease progression rates were lower in reports of Brabander et al. [8] (12%) and Sitani et al. [13] (10%).

While the short-term results from the NETTER group were substantially better in terms of PFS that was not reached for the patients receiving177Lu-PRRT, our long-term data estimated a median PFS of 48 months. Moreover, the results were well in line with our previous long-term report (PFS 46 months; 95% CI: 41 – 58 months) [9].

In NETTER-1 trial, the median PFS was not attained due to the short follow-up duration, but the determined cumulative PFS at 20 months was 65.2%. Swiha et al. [20] and our study demonstrated a similar estimated PFS at 20 months of 67.4% and 79.5%, respectively. Similar to our previous report on 177Lu-PRRT (46 mo) and that of Swiha at al. (34.1 mo) [20] and Demirci et al. (36.4 no) [11], we observed a longer median PFS of 48 months. Similar to the OS, the common factor predicting the PFS was the presence of bone metastases. As per our clinic protocol, patients were treated with an average total cumulative 177Lu-DOTATATE dose of 44 GBq per patient over 8-9 cycles and 2 years (mean 5.92 GBq/cycle) which is longer, compared to that of NETTER 1 protocol where fixed doses of 7.4 GBq were administered at 2 monthly intervals within a period of 1 year. The long treatment period may be one possible factor to impact the prolonged PFS.

PRRT also played a role in the Grade III NETs (DCR: 12/18) with an OS of 48 months and PFS of 30 months. The results tie in well with the study by Demirci et al. [11], who exclusively gave on long-term survival update in WHO Grade 3 NETs wherein the mean OS was 55 months and PFS was 36.4 months. This critical finding supports the role of 177Lu-PRRT even in Grade 3 NETs with high SSTR expression.

Side effects from PRRT are well known and mainly comprise of renal and haematological toxicity. Our long-term toxicity results are consistent with our previous short-term and long-term reports and other long-term results showing similar delayed side effects of treatment.

Myelodysplastic Syndrome (MDS) occurred in two patients (0.8%) and leukemic in one patient, with approximately 1.3% of the pa-

tient cohort at risk of developing MDS/Leukemia. Brabander et al. [8], observed MDS in 1.5% (9/443). Baum et al. [12], Brabander et al. [8], Bodei et al. [22], and Kesavan et al. [23] identified MDS/leukemia of 2.1%, 2.2%, 2%, and 1.4%. No G3/4 kidney toxicity was identified, but hepatotoxicity was present in patients with a high liver disease burden.

This study has several limitations: a retrospective, lack of randomization, and treatment offered to patients were non-uniform. However, unlike trial settings, the data was based on a real-world clinical setting scenario.

10. Conclusions

This study confirms the findings of our earlier short-term and long-term reports, demonstrating promising survival outcomes, therapeutic efficacy, and low prevalence of delayed toxicity for 177Lu-PRRT in GEP-NETs. The study also provides evidence of the improved quality of life in multiple domains. Prevalence of bone metastases, and 177Lu-PRRT refractory disease significantly impact the survival.

References

1. .Rinke A, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumour growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol. 2009; 27: 4656-63.
2. Delavault P, Caplin ME, Liyanage N, Blumberge J. The CLARINET study: Assessing the effect of lanreotide autogel on tumor progression-free survival in patients with nonfunctioning gastroenteropancreatic neuroendocrine tumors. J Clin Oncol. 2017; 30.
3. Yao JC, Shah MH, Ito T, et al. RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011; 364: 514–23.
4. Kwekkeboom DJ, Mueller-Brand J, Paganelli G, Anthony LB, Pauwels S, Kvols LK, et al. Overview of results of peptide receptor radionuclide therapy with 3 radiolabeled somatostatin analogs. J Nucl Med. 2005; 46: 62-6.
5. Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 trial of 177Lu-DOTATATE for midgut neuroendocrine tumors. N Engl J Med. 2017; 376: 125–35.
6. Wang LF, Lin L, Wang MJ, Li Y. The therapeutic efficacy of 177Lu-DOTATATE/DOTATOC in advanced neuroendocrine tumors: A meta-analysis. Medicine (Baltimore). 2020; 99: e19304.
7. Zhang J, Song Q, Cai L, Xie Y, Xie Y. The efficacy of 177Lu-DOTATATE peptide receptor radionuclide therapy (PRRT) in patients with metastatic neuroendocrine tumours: a systematic review and meta-analysis. J Cancer Res Clin Oncol. 2020; 146: 1533-43.
8. Brabander T, van der Zwan WA, Teunissen JJM, Kam BLR, Feelders RA, Feelders RA, et al. Long-Term Efficacy, Survival, and Safety of [177Lu-DOTA0,Tyr3]octreotate in Patients with Gastroenteropancreatic and Bronchial Neuroendocrine Tumors. Clin Cancer Res. 2017; 23: 4617-24.
9. Ballal S, Yadav MP, Damle NA, Sahoo RK, Bal C. Concomitant 177Lu-DOTATATE and Capecitabine Therapy in Patients With Advanced Neuroendocrine Tumors: A Long-term-Outcome, Toxicity, Survival, and Quality-of-Life Study. Clin Nucl Med. 2017; 42: e457-66.
10. Kunikowska J, Pawlak D, Bąk MI, Kos-Kudła B, Mikołajczak R, Królicki L. Long-term results and tolerability of tandem peptide receptor radionuclide therapy with 90Y/177Lu-DOTATATE in neuroendocrine tumors with respect to the primary location: a 10-year study. Ann Nucl Med. 2017; 31: 347-56.
11. Demirci E, Kabasakal L, Toklu T, Ocak M, Şahin OE, Alan-Selcuk N. 177Lu-DOTATATE therapy in patients with neuroendocrine tumours including high-grade (WHO G3) neuroendocrine tumours: response to treatment and long-term survival update. Nucl Med Commun. 2018; 39: 789-96.
12. Baum RP, Kulkarni HR, Singh A, Kaemmerer D, Mueller D, Prasad V, et al. Results and adverse events of personalized peptide receptor radionuclide therapy with 90Yttrium and 177Lutetium in 1048 patients with neuroendocrine neoplasms. Oncotarget. 2018; 9: 16932-50.
13. Sitani K, Parghane RV, Talole S, Basu S. Long-term outcome of indigenous 177Lu-DOTATATE PRRT in patients with Metastatic Advanced Neuroendocrine Tumours: a single institutional observation in a large tertiary care setting. Br J Radiol. 2021; 94: 20201041.
14. Common Terminology Criteria for Adverse Events (CTCAE) v5.0 2017.https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf.Food and Drug Administration. Guidance for Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical. Accessed September 17, 2021.
15. Gupta SK, Singla S, Thakral P, Bal CS. Dosimetric analyses of kidneys, liver, spleen, pituitary gland, and neuroendocrine tumors of patients treated with 177Lu-DOTATATE. Clin Nucl Med. 2013; 38: 188-94.
16. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. J Nucl Med. 2009; 50: 122-50.
17. Crooks V, Waller S, Smith T, Hahn TJ. The use of the Karnofsky Performance Scale in determining outcomes and risk in geriatric outpatients. J Gerontol. 1991; 46: 139-44.
18. Kavecansky J, Wei L, Caronia L, Ramirez MT, Bloomston M, Shah MH. Bone metastases in well-to-moderately differentiated neuroendocrine tumors: a single institutional review from the Ohio State University Medical Center. Pancreas. 2015; 44: 198-203.
19. Abou Jokh Casas E, Pubul Núñez V, Anido-Herranz U, Garrido Pumar M, Cameselle-Teijeiro JM, Hilal A, et al. Evaluation of

177Lu-Dotatate treatment in patients with metastatic neuroendocrine tumors and prognostic factors. World J Gastroenterol. 2020; 26: 1513–24.

20. Swiha MM, Sutherland DEK, Sistani G, Khatami A, Abazid RM, Mujoomdar A, et al. Survival predictors of 177Lu-Dotatate peptide receptor radionuclide therapy (PRRT) in patients with progressive well-differentiated neuroendocrine tumors (NETS). J Cancer Res Clin Oncol. 2021; 148: 225-6
21. Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol. 2008; 26: 2124-30.
22. Bodei L, Modlin IM, Luster M, Forrer F, Cremonesi M, Hicks RJ, et al. Myeloid neoplasms after chemotherapy and PRRT: myth and reality. Endocr Relat Cancer. 2016; 23: C1-7.
23. Kesavan M, Turner JH. Myelotoxicity of Peptide Receptor Radionuclide Therapy of Neuroendocrine Tumors: A Decade of Experience. Cancer Biother Radiopharm. 2016; 31: 189-98.