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Survival Outcomes in Metastatic Gastroenteropancreatic Neuroendocrine Tumor Patients receiving Concomitant ^{225}Ac-DOTATATE Targeted Alpha Therapy and Capecitabine: A Real-world Scenario Management Based Long-term Outcome Study

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Abstract

Rationale: Although the short-term results of targeted alpha therapy (TAT) with ^{225}Ac-DOTATATE in gastroenteropancreatic neuroendocrine tumors (GEP-NETs) have proven effective, none have assessed the long-term outcome results. In this study, we aimed to evaluate the long-term outcome of ^{225}Ac-DOTATATE targeted alpha therapy (TAT) in patients with somatostatin receptor (SSTR)-expressing advanced-stage metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

Methods: Patients with ^{68}Ga-DOTANOC PET/CT scans showing moderate-to-high SSTR expression were recruited. Systemic TAT was performed in 91 adults with GEP-NET [54 males, and 37 females] mean age 54 years (y) (range: 25-75y)] using ^{225}Ac-DOTATATE (100-120 kBq/kg body weight). All patients were given capecitabine therapy as a radiosensitizer (dose 2 g/day) from day 0 to 14 of every ^{225}Ac-DOTATATE treatment cycle**.** Patients were categorized into three groups based on the status of prior ^{177}Lu-PRRT: prior ^{177}Lu-PRRT-refractory-group; prior ^{177}Lu-PRRT-disease-control group; and ^{177}Lu-PRRT naïve group. Primary endpoints were overall survival (OS), and secondary endpoints included progression-free survival (PFS), objective tumour response, clinical response, and the assessment of treatment-related toxicities.

Results: Among the 91 patients, 57 underwent prior ^{177}Lu-DOTATATE therapy [24 disease controlled (PR/SD), 33 progressive diseases (PD)]. A total of 453 ^{225}Ac-DOTATATE TAT cycles were administered [median four cycles per patient; range 1-10] in a median follow-up duration of 24 months (range 5-41mo). Median OS was not attained with a 24-month overall survival probability of 70.8%. In multivariate analysis, prognostic factors associated with a poor OS included, the presence bone metastases [HR: 2.501; 95% CI: 1.826 - 5.791; P<0.032], and ^{225}Ac-DOTATATE therapy refractory disease [HR: 8.781; 95% CI: 3.843 - 20.062; P<0.0001]. Median PFS was also not reached with a 24-month progression-free survival probability of 67.5%. The multivariate analysis revealed only ^{177}Lu-PRRT refractory disease significantly associated with a reduced PFS. [HR: 14.338; 95% CI: 1.853 - 97.698; P = 0.011]. Two of 79 patients (2.5%) with assessable disease experienced complete response; 38 (48%) had a partial response, 23 (29%) had SD, and 16 (20.2%) had PD. PD was observed in more patients from the prior ^{177}Lu-PRRT-refractory group (11/33; 34%) as compared to ^{177}Lu-PRRT-naïve patients (4/24; 11%), P-0.056. Patients from the prior ^{177}Lu-PRRT-refractory group had the highest risk of poor PFS [HR:13.91; 95% CI: 4.45 - 42.271; P = 0.0009]. A significant clinical benefit was achieved post ^{225}Ac-DOTATATE therapy with minimal treatment-related toxicities.

Conclusion:. The long-term results reveal ^{225}Ac-DOTATATE TAT has shown promising results and improves overall survival, even in patients refractory to prior ^{177}Lu-DOTATATE treatment, with transient and acceptable adverse effects.

Keywords: ^{225}Ac-DOTATATE TAT, GEP-NETs, Overall survival, Progression-free survival, Objective response

Introduction

Expanded treatment options have recently become available to patients with well-differentiated gastroenteropancreatic (GEP) neuroendocrine tumors (NETs) [1]. Surgery offers the best chance of curing patients with localized GEP-NETs; however, surgery is not feasible when extensive metastases are present. In such cases, other options include somatostatin analogues (SSAs; e.g. lanreotide and octreotide), [2,3] interferons, tyrosine kinase inhibitors (e.g. sunitinib), [4] mammalian target of rapamycin (mTOR) inhibitors (e.g. everolimus), [5] peptide receptor radionuclide therapy (PRRT), [6] systemic chemotherapy, and liver-targeted therapies, depending on the extent, stage, and location of disease, and tumour grade [7]. The phase III NETTER-1 trial provided evidence for the efficacy and safety of PRRT using lutetium-177 (^{177}Lu) in this setting [8]. However, only 18% of patients achieve a partial or complete response, despite treatment with ^{177}Lu-DOTATATE, a beta- and gamma-emitting radionuclide, and most patients relapse within 2−3 years of treatment [9,10].

One promising option that has gained interest is using high linear energy transfer (LET) alpha-emitting radioisotopes such as Actinium-225 (^{225}Ac) and Bismuth-213 (^{213}Bi) instead of low LET beta-emitting radioisotopes like Yttrium-90 (^{90}Y) and ^{177}Lu. The theoretical physical advantages of alpha radiation over beta radiation is an enduring option to further improve the efficacy of PRRT by labelling the peptides with alpha-particle emitters [11].

Results from preclinical and clinical studies have suggested that an alternative strategy using PRRT delivering an alpha-emitting radionuclide such as ^{213}Bi and ^{225}Ac-DOTATOC may have promise in patients with advanced GEP-NETs refractory to ^{177}Lu-PRRT [12-16].

One clinical study using ^{213}Bi-DOTATOC has been reported in seven patients with NETs whose disease had progressed on beta-PRRT [17]. Although that study demonstrated the therapeutic potential of this approach, ^{213}Bi-DOTATOC was administered via intra-arterial delivery, limiting the more widespread application of alpha-radionuclide therapy in the real-world setting. ^{213}Bi also has a physical half-life of only 46 minutes resulting in logistical challenges for broader adoption.

These studies prompted us to investigate the role of ^{225}Ac-DOTATATE as salvage treatment for patients with GEP-NETs [18]. Initial results from 32 patients who had previously received ^{177}Lu-PRRT indicated that ^{225}Ac-DOTATATE administered intravenously induced sustained responses. Approximately two-thirds of the 24 patients (15/24, 62.5%) who underwent interim morphological response analysis had a partial response (PR), and the disease control rate

(DCR) was 100% [15 PRs, and nine stable diseases (SD)]. Furthermore, there was no documented progressive disease (PD), and no deaths occurred during a median follow-up of 8 months (range 2−13 months). We observed minimal and reversible toxicities and no life-threatening adverse events (AEs). These data suggested that multiple cycles of therapy could be safely administered without a significant risk of either acute or delayed radiation toxicity [18]. Despite the favourable short-term results, as far as the authors are aware, no comprehensive long-term outcome results have been extensively studied to demonstrate the survival benefit of ^{225}Ac-DOTATATE therapy in both prior ^{177}Lu-PRRT and PRRT naïve groups of GEP-NET patients.

Hence, in the current study, we extensively studied the long-term follow-up data in an expanded cohort of patients to assess overall survival (OS), progression-free survival (PFS), factors predicting the survival, response to treatment, and evaluated the patterns of delayed adverse event profile in advanced metastatic GEPT-NETs.

Materials and Methods

Study Design

The independent institutional review board of All India Institute of Medical Sciences, India approved this study. All patients provided written informed consent before participation in the study. The study design and treatment regimen are depicted schematically in Fig. 1. The detailed methodology is incorporated in the supplementary information.

This study was conducted in patients with histologically well-differentiated, inoperable, or metastatic GEP-NETs. Patients were included if they had a history of prior concomitant therapies, such as SSAs and chemotherapy, as well as ^{177}Lu-DOTATATE therapy. Essential prerequisites were significant somatostatin receptor (SSTR) expression and at least one measurable lesion on the computed tomography (CT) component of the baseline gallium ^{68}Ga-DOTANOC positron-emission tomography (PET)/CT scan (uptake ≥liver, or Krenning score ≥2, compared on maximum intensity projection, coronal and transaxial images).

Patients with inadequate laboratory parameters (baseline haemoglobin <9 g/dL, platelet count <75,000/μL, serum creatinine >1.6 mg/dL, serum bilirubin >3 mg/dL), and Karnofsky performance status (KPS) <40 were excluded.

Treatment Planning and Follow-up

Image Acquisition

All patients underwent a baseline diagnostic ^{68}Ga-DOTANOC PET/CT scan as a pre-therapeutic work-up. For morphological assessment, additional ^{68}Ga-DOTANOC PET/CT scans were repeated within 6 to 8 weeks after completing every 2 to 3 cycles of ^{225}Ac-DOTATATE TAT, or patients presenting with clinical disease progression, or at the investigator's discretion.

^{68}Ga-DOTANOC PET/CT Imaging

The ^{68}Ga-DOTANOC PET/CT scans did not require special preparation. A mean activity of 111 MBq (3 mCi) was injected and PET/CT scans were acquired between 45 to 60 minutes post injection. For acquisition, the patient lied in supine position on the exam table. The acquisition protocol constituted an initial scout image to define the field of view from vertex to mid-thigh, followed by diagnostic CT and PET scans. The diagnostic whole body CT scan parameters involved a diagnostic dose CT with 300–380 mAs, 120 kVp, slice thickness 3.75 mm, and pitch 0.6. Additionally, spot views were acquired if required with a slice thickness of 1.25 mm on CT at 120 kVp, 300-380 mAs, and a pitch of 0.6.

Administration and the route of contrast depended on the site of the tumor and scan indication. Generally, CT scans acquisitions were acquired with non-ionic, isomolar contrast medium (Iodixanol Injection USP - 1 ml/kg body weight) containing 320 mg I/ml intravenously (I.V) or orally and neutral oral contrast (water). In our study, 56 patients were injected with non-ionic, isomolar contrast medium. Positive oral (Iodixanol) and neutral contrast (water) was administered when indicated. All tumors were visualized on the diagnostic CT scan, but only tumors with measurable dimensions according to RECIST 1.1 criteria were included for the assessment of morphological response.

Treatment

Long and short-acting somatostatin agents were stopped 4 to 5 weeks and 48 to 72 hours, respectively, before ^{225}Ac-DOTATATE therapy. Pre-medications, including an antiemetic (ondansetron) and/or corticosteroid (dexamethasone), were administered and repeated if necessary. For kidney protection, a single-day kidney protection protocol was followed, which consisted of lysine (23.3 g) and arginine (8 g) in 1 L of the amino acid mixture in water for injection solution. This cocktail was infused over 4 hours, starting 30 to 60 minutes before the ^{225}Ac-DOTATATE infusion.

As previously described, ^{225}Ac-DOTATATE (100-120 kBq/kg body weight per cycle [3-3.2 µCi/kg] diluted in 50 mL of saline was administered over 30 minutes (flow rate 1.6 mL/min) every eight weeks up to a maximum cumulative dose of 111 MBq [3 mCi]. All patients received capecitabine as a radiosensitizer (1 g orally twice daily) from day 0 to 14 of every cycle. Patients were monitored for 24 hours after ^{225}Ac-DOTATATE TAT to observe any acute side effects. Patients on supportive care or sandostatin continued to receive those treatments at the investigator's discretion.

Withdrawal from the study occurred in the event of any serious adverse events (SAE); lack of adherence to the treatment protocol due to unavoidable pandemic conditions; demonstrated disease progression; withdrawal of consent for further treatment cycles; or death.

Assessments

Safety monitoring was performed at baseline and at 8-week intervals thereafter. Assessments included physical examination, vital parameters, laboratory tests (assessed at 2, 4, and 6 to 8 weekly intervals), and clinical evaluation via KPS and Eastern Cooperative Oncology Group (ECOG) performance status (PS). Patients were given a diary in which they could document any side effects or discomfort. With the exception of blood parameters, all other assessments were conducted at baseline and at eight weeks after each cycle of ^{225}Ac-DOTATATE TAT, or upon withdrawal from the study, or at treatment completion.

Patient groups

Based on the history of ^{177}Lu-PRRT patients were categorized as the prior ^{177}Lu-PPRT (prior-^{177}Lu) and ^{177}Lu-PRRT-naïve (^{177}Lu-PRRT naïve) groups (Fig. 2). The prior ^{177}Lu-PRRT group was further divided according to cancer status after ^{177}Lu-PRRT, i.e., those who were treatment-refractory and those who were stable or responded to ^{177}Lu-PRRT (Fig. 2). The details of groups are explained below:

- **Prior ^{177}Lu-PRRT-refractory group:** Patients progressed during the ^{177}Lu-DOTATATE treatment course or within in 12 months of completion of ^{177}Lu-DOTATATE treatment regimen. (n = 33)
- **Prior ^{177}Lu-PRRT-disease-control group:** Patients completed the ^{177}Lu-DOTATATE treatment regimen and achieved disease control (partial response or stable disease), but were further treated with ^{225}Ac-DOTATATE due to the persistent high tumor burden. (n = 24)
- **^{177}Lu-PRRT naïve group:** Patients did not receive ^{177}Lu-DOTATATE therapy at any point of the treatment course. (n = 34)

Outcomes

The primary endpoint was OS (defined as the time from initiation of ^{225}Ac-DOTATATE TAT until death due to any cause or the date of the last contact). Patients with lost follow-up were considered alive but were censored) (Supplementary material). The key secondary endpoint was PFS (defined as the first observation of documented morphological disease progression on diagnostic CT according to the assessment by Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) [19] or the development of pleural/pericardial effusion/malignant ascites, or disease-specific death (DSD), whichever occurred first. Other co-secondary endpoints included objective tumour response by RECIST v1.1 clinical response, clinical response assessment with KPS and ECOG PS [20], and evaluation of the treatment related adverse events (AEs) using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) and The Food and Drug Administration (FDA) document entitled "Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials [21,22].

Statistical Analysis

Univariate analysis was used to compare characteristics between patient groups. Based on the normality of parameters, continuous variables with normal distribution were represented as mean, standard deviation, range, median, and interquartile range (IQR). Comparisons between parameters of the same population at different time points were analysed using a paired *t*-test (parametric test) or Wilcoxon signed-rank test (non-parametric test). OS and PFS plots were constructed using the Kaplan-Meier methodology; a log-rank test was used to compare survival between the groups. Cox proportional hazards regression model was carried out to determine the predicitive and prognostic factors associated with OS and PFS. P-values <0.05 were considered to be significant. The analysis was conducted using MedCalc statistical software (version 15.1; MedCalc Software Ltd, Ostend, Belgium).

Results

Baseline Demographic and Clinical Characteristics of Patients

Between April 2018 and February 2022, 91 consecutive GEP-NET patients (37 women, 54 men, mean±standard deviation age: 54.3±11.6 years, range; 25–75 years) were enrolled. The first ^{225}Ac-DOTATATE TAT treatment was administered in April 2018, and the last patient was recruited in October 2021. The last date for follow-up cut-off was February 20, 2022. The median follow-up duration was 24 months (range: 5 - 41 months) from the start of ^{225}Ac-DOTATATE TAT.

Baseline characteristics are summarised in Table 1. The pancreas (33%) was the most common site of the primary tumour in patients, followed by the duodenum (14.3%) and ileum (13%). NETs were World Health Organization grade 1 in 33 (36.2%), grade 2 in 48 (52.7%), and grade 3 in 7 (7%) patients (Table 1 and Supplemental Table 1). Primary/residual tumor was noted in 55 patients (60.4%) and all patients demonstrated metastases on SSTR PET/CT scan, with the most common metastatic sites being the liver (n = 88; 96.7%), lymph nodes (n = 66; 72.5%), and bone (n = 25; 27.5%) (Supplemental Table 2). Eighteen patients (20%) had received prior chemotherapy (Supplemental Table 3), most of whom had one previous line (n =12; 66.6%); four patients (22.2%) had two prior lines, and two (11%) had ≥3 prior lines. Ten symptomatic patients were on long-acting SSAa which were stopped 4 weeks before commencing ^{225}Ac-DOTATATE-TAT.

Treatment

The mean cumulative radioactivity administered was 35.52 MBq (range: 21.64 - 59.47 MBq [960 µCi, IQR: 600 - 1608 µCi]). The median interval between treatment cycles was 8 weeks. A total of 453 cycles of ^{225}Ac-DOTATATE TAT were administered: 32 patients received 1 to 3 cycles, and the remaining 59 patients received 4 to 10 cycles (Supplemental Table 4). Three patients received a single cycle of ^{225}Ac-DOTATATE TAT: one died after the first cycle, one was lost to follow-up, and the third patient withdrew consent.

Efficacy Assessment

OS and PFS

Twenty-six patients (26.5%) died during follow-up. The details of the causes of death are detailed in Supplemental Table 5. In the overall patient population, the median OS was not attained with a 24-month survival probability of

70.8% (Fig. 3A). On sub-categorical analysis, while 16 (16/33; 48.5%) deaths occurred in the prior ^{177}Lu-PRRT-refractory group (median OS of 26 months), three (3/24, 12.5%) and seven deaths (7/34; 20.6%) occurred in the prior ^{177}Lu-PRRT-disease-control group and ^{177}Lu-PRRT naïve group, respectively (P-0.0003) (Fig. 3B). Interestingly, in patients who demonstrated disease control on ^{177}Lu-PRRT, none of the three deaths was disease-specific (Supplemental Table 5). Patients in the prior ^{177}Lu-PRRT-disease-control group showed a significantly better OS results compared to even better the ^{177}Lu-PRRT native group (95% vs 67%) (Fig. 2). We speculated these difference might be due to inherent differences in the baseline demographic/clinical characteristics of the patient cohorts. However, univariate comparison between the groups did not reveal any difference in the demographic parameters (Supplemental Table 6).

On univariate analysis, the presence of bone metastases (Fig. 3C), cumulative dose of ^{225}Ac-DOTATATE TAT <37,000 KBq (Fig. 3D), and progressive disease to ^{225}Ac-DOTATATE TAT **(**Fig. 3E) were associated with significantly poorer OS (Supplemental Table 7). However, on multivariate analysis the presence of bone metastases [HR: 2.501; 95% CI: 1.826 - 5.791; P = 0.032], and ^{225}Ac-DOTATATE therapy refractory disease (PD) persisted as significant prognostic factors associated with poor OS [HR: 8.781; 95% CI: 3.843 - 20.062; P <0.0001] (Fig. 3E).

At the time of this analysis, median PFS was not attained in the overall patient population. The median PFS was 30 months in the prior ^{177}Lu-PRRT-refractory group and was not reached in the prior ^{177}Lu-PRRT-disease-control group (HR: 13.553; 95% CI: 4.343 - 42.271; P = 0.0009) (Fig. 4A). Similarly, univariate analysis revealed an association between the presence of bone metastases (Fig. 4B) and cumulative ^{225}Ac-DOTATATE dose of <1 mCi and PD (HR: 2.718; 95% CI: 0.999 - 7.393; P = 0.028) (Fig. 4C) (Supplemental Table 8). However, on multivariate analysis, the only ^{177}Lu-PRRT refractory disease was significantly associated with a significantly reduced progression-free survival. [HR: 14.3; 95% CI: 1.853 - 97.6; P = 0.011]

Objective Response

Morphologic response to ^{225}Ac-DOTATATE TAT according to the disease status on prior ^{177}Lu-PRRT therapy is shown in table 2. Two of the 79 evaluable patients (2.5%), both previously treated with ^{177}Lu-PRRT, had a complete response (CR); no CRs were observed in the ^{177}Lu-PRRT naïve group. ^{68}Ga-DOTANOC PET/CT scans revealed partial response in 38 (48%), and SD in 23 patients (29%), for a DCR of 80%. Twelve and four progression events

occurred in the prior-^{177}Lu-PRRT and ^{177}Lu-PRRT naïve groups, respectively, representing a 40% lower estimated risk of progression in the ^{177}Lu-PRRT naïve group than in the prior-^{177}Lu-PRRT group.

In the prior-^{177}Lu-PRRT group among 24 patients who either experienced disease-control with ^{177}Lu-PRRT, 17 (74%) further showed response to ^{225}Ac-DOTATATE TAT. Promising response rates were also observed in eight of 30 patients (27%; 1 CR and 7 PRs) belonging to the prior ^{177}Lu-PRRT-refractory group, with SD in a further 11 patients (36.6%; Fig. 1). PRs were observed in 15 of 27 patients (55.5%) in the ^{177}Lu-PRRT naïve groups.

Of the 17 patients with PD, 14 experienced disease-specific deaths, two have been re-challenged with an escalated dose of 150 kBq/kg ^{225}Ac-DOTATATE and have shown disease stability, and the remaining one patient refused to undergo any further treatment but is alive.

Clinical Response

Among the patients who were alive till the end of analysis, the median KPS significantly improved from 60 at baseline to 70 after treatment ($P < 0.0001$), and the median ECOG score enhanced from 2 to 1 ($P<0.0001$). In the overall population, while the KPS improved from 60 to 70 ($P = 0.053$), ECOG states remained same as the median baseline values of 2.

Toxicity and Adverse Events

Treatment-related AEs occurring during ^{225}Ac-DOTATATE TAT is shown in Supplemental Table 9. No renal or liver toxicity was observed. No tumour-lysis syndrome was observed in any patient. One patient had grade 3 thrombocytopenia. Clinical disease-related symptoms, such as fatigue, loss of appetite, nausea, gastritis, abdominal pain, abdominal distension, and myalgia, were mainly caused by the nature of cancer and site of metastasis and were prevalent before the initiation of ^{225}Ac-DOTATATE treatment. All the above symptoms improved after treatment.

Malignant ascites and pleural effusion, which are signs of PD, were observed in 14 and 2 patients, respectively. Grade 1/2 malignant ascites were present in eight patients at baseline. Eventually, four patients experienced grade 2, and 10 experienced life-threatening malignant ascites and died. One patient with pleural effusion also died.

Before initiation of ^{225}AC-DOTATATE, flushing was documented in eight patients, of which three had grade 3 flushing. After treatment, flushing improved to grade 1 in all patients.

Transient symptoms, including nausea, vomiting, and abdominal discomfort, were encountered in most patients during the amino acid infusion and ^{225}Ac-DOTATATE administration and settled within 24 hours after treatment. Fatigue, myalgia, and loss of appetite were also observed and resolved within one week after treatment.

Discussion

In our short-term analysis on the first clinical experience of the alpha-emitting conjugate ^{22}Ac-DOTATATE TAT in 32 patients with GEP-NET who had exhausted or were refractory to beta-emitting ^{177}Lu-DOTATATE therapy, we observed favourable responses with low toxicities [18]. The current study reports findings from an expanded cohort of 91 patients with an extended median follow-up of 24 months, ranging from 5 to 41 months. Our results provide further evidence that ^{225}Ac-DOTATATE is effective in patients with NETs, a group with few therapeutic options, especially after progression on other therapies. In the current study, median overall survival and progression-free survival were not attained. The ORR and DCR were 48% and 80%, respectively, and was lower than our previously reported short-term data showing a response rate of 63% and DCR of 100%.

Though the current study has broad and heterogenous inclusion criteria, it was conducted in a real-world setting based on everyday clinical practice where patients of poor performance status (31%) (ECOG status ≥3) were included, which is a critical and optimistic perspective of this study. We believe that real-world based clinical study results can be extended and translated to the general population. Moreover, in this study, several demographic and clinical variables were compared between the three groups of patients who were categorized based on the status of prior ^{177}Lu-PRRT therapy and matched (Supplemental Table 6), which ruled out the potential inherent bias.

Comparisons with the NETTER-1 long-term overall survival results [23] showing a median OS of 48 months revealed that ^{225}Ac-DOTATATE provided an additive overall survival benefit of 26 months in the worst outcome patient cohort who were refractory to prior ^{177}Lu-PRRT. Well in line with the phase III NETTER-1 [8] short-term results which reported 12% (14/116) deaths in NET patients who underwent 177Lu-DOTATATE therapy as a first-line treatment option, our cohort of 34 ^{177}Lu- PRRT naïve patients reported a similar disease-specific death rate of 11.7% (4/34) in a median follow-up of 24 months.

Another finding that merits comment is that in this cohort of patients from our and the NETTER 1 group, the median OS was not attained. An interpretation of these findings is that the upfront use of ^{225}Ac-DOTATATE therapy in

advanced NETs is may not be necessary as a mainstay option. Irrespective of the disease burden, patients can be first challenged with ^{177}Lu-PRRT and eventually be re-challenged with alpha based ^{225}Ac-DOTATATE therapy in situations where there is the persistence of high disease burden despite attaining maximum tolerable dose of Lutetium-177 (~1.2 Ci), or the patient is refractory to ^{177}Lu-PRRT.

Patients (n = 24) who achieved disease-control (PR/SD) with prior ^{177}Lu-PRRT followed by retreatment with ^{225}Ac-DOTATATE showed the best outcome with a 24-month OS probability of 95%, which was remarkably higher compared to the ^{177}Lu-PRRT refractory (55.6%) and naïve (62.6%) groups. Moreover, only three deaths occurred in this group of patients, and none of the events was disease-specific. There may be two possible explanations for these findings; firstly, ^{225}Ac-DOTATATE has significantly increased the overall survival as an adjuvant treatment option after ^{177}Lu-PRRT. Alternatively, it could simply mean that patients have already achieved disease-control on ^{177}Lu-PRRT and can be followed up with a "wait and watch" approach until there is an occurrence of disease progression. However, only a double-arm RCT between wait and watch approach group versus further treatment with ^{225}Ac-DOTATATE group can be the definitive answer.

Rudisile et al. [24] studied the outcomes of ^{177}Lu-PRRT retreatment in the salvage setting for all patients who responded to the initial standard 4 cycles of ^{177}Lu-PRRT. They observed an additional response rate of 3%, PFS of 6 months, and OS of 51 months. The largest systematic review and meta-analysis by Strosberg et al. [25] examined published evidence of PRRT re-treatment efficacy and safety in patients with advanced progressive neuroendocrine tumors. They have demonstrated that ^{177}Lu-PRRT re-treatment provided encouraging results with a median PFS of 12.5 mo and a median OS of 26.7 mo. In a similar salvage treatment setting our results go beyond the previous reports as we observed remarkably higher response rates of 74% (17/23; CR/PR) and promisingly prolonged survival benefits as both PFS and OS were not attained with ^{225}Ac-DOTATATE therapy.

While, several groups report variations in the site of metastases associated with poor survival, it is apparent that presence of distant metastases has a significant impact on the survival irrespevtive of the treatment modality. Regarding, the impact of bone metastases on the survival, our results with ^{225}Ac-DOTATATE TAT are similar to those reported by Rudisile et al. [24] and Swiha et al. [26] who demonstrated the presence of bone metastases was associated with a shorter OS in patients with well-differentiated NETs who received ^{177}Lu-DOTATATE.

In addition to morphologic responses, improvements in overall patient well-being were observed, with the median KPS increasing from 60 before treatment (patient requiring medical care and much assistance with self-care) to 70 post-treatment (the patient being able to care for themselves but being unable to do their usual activities or active work). This highlights the potential of ^{225}Ac-DOTATATE on improving the quality of life in the worst-outcome patient population.

Treatment with ^{225}Ac-DOTATATE TAT was well tolerated. As previously described, low-grade hematologic AEs were the most common side effect of treatment with ^{225}Ac-DOTATATE. Grade 3 and higher AEs were uncommon and transient or unlikely to be treatment-related. The total amount of Actiniun -225 administered up to 111 MBq did not correlate with AEs. Interestingly, AEs were also not correlated with ^{177}Lu-naïve or prior-^{177}Lu therapy which suggests that dosing with ^{225}Ac-DOTATATE TAT should not be influenced by prior treatment with ^{177}Lu. Moreover, similar to the short-term results [18] by our group on ^{225}Ac-DOTATATE, haematological, kidney, and liver function toxicities were minimal, but over the time in the long-term follow-up we compared to our pilot results, we observed a significantly high incidence of malignant ascites and pleural effusion; whether it is related to disease *per se* or TAT-related longer follow-up of this cohort shall clarify. In agreement with our findings, another study using ^{225}Ac-DOTATOC reported that cumulative doses of 60,000-80,000 kBq were tolerated with minimal acute and chronic grade 3/4 hepatotoxicity in patients with advanced-stage malignancies [27]. Looking at the toxicity profile, it seems that we have a scope of further escalating the individual activity/kg or even higher cumulative activity in future. Thus, the only approach is to rigorously follow these patients for long-term side effects of ^{225}Ac-DOTATATE TAT.

High-level evidence for long-term safety and sustained OS and radiological PFS benefits in patients with GEP-NET treated with ^{225}Ac-DOTATATE are crucial and warrant well-controlled, multicenter randomised controlled trials to determine its role and the best treatment algorithm for this challenging disease.

Limitations

Our results are exploratory, single-centre, and consist of a heterogeneous patient population. Although not conducted as a clinical trial with strict inclusion criteria, we believe the study has the advantage of the largest GEP-NET patient population cohorts treated with ^{225}Ac-DOTATATE therapy, which included poor outcome patients and better reflect the results of treatment-related toxicity, confirm the benefit of efficacy, survival, and improvement in the quality of

life in the real-world clinical settings. Though all the CT scans of the PET/CT component were of diagnostic quality, contrast was not administered in all patients resulting in suboptimal quality images.

In conclusion, ^{225}Ac-DOTATATE-based PRRT was effective in the heavily pre-treated GEP-NET cohort of patients, with good survival rates, high response rates, improvements in KPS, and an acceptable toxicity profile. ^{225}Ac-DOTATATE TAT may be a suitable treatment option for patients with SD or PD following ^{177}Lu-DOTATATE beta-therapy. Pateints refractory to ^{225}Ac-DOTATATE treatement are have the worst outcome. We strongly advocate a multicenter large randomised controlled trial to assess the potential of this strategy as a new therapeutic paradigm for patients with GEP-NET who have exhausted all other options. Further, a balanced approach by exploiting our long-term results and clinical trials can best aid the oncology community to deliver the best benefit to the patient community with individualized patient-based cancer care.

Disclosure: **The authors have nothing to disclose**

KEY POINTS

QUESTION: what is the long-term outcome of GEP-NET patients treated with ^{225}Ac-DOTATATE targeted alpha therapy?

PERTINENT FINDINGS: The median OS was not attained and the 24-month overall survival probability was 70.8%. Median PFS was also not reached with a 24-month progression-free survival probability of 67.5%. A significant clinical benefit was achieved post ^{225}Ac-DOTATATE therapy with minimal treatment-related toxicities.

IMPLICATIONS FOR PATIENT CARE: The long-term results reveal ^{225}Ac-DOTATATE TAT has shown promising results, even in patients resistant to prior ^{177}Lu-DOTATATE, with transient and acceptable adverse effects.

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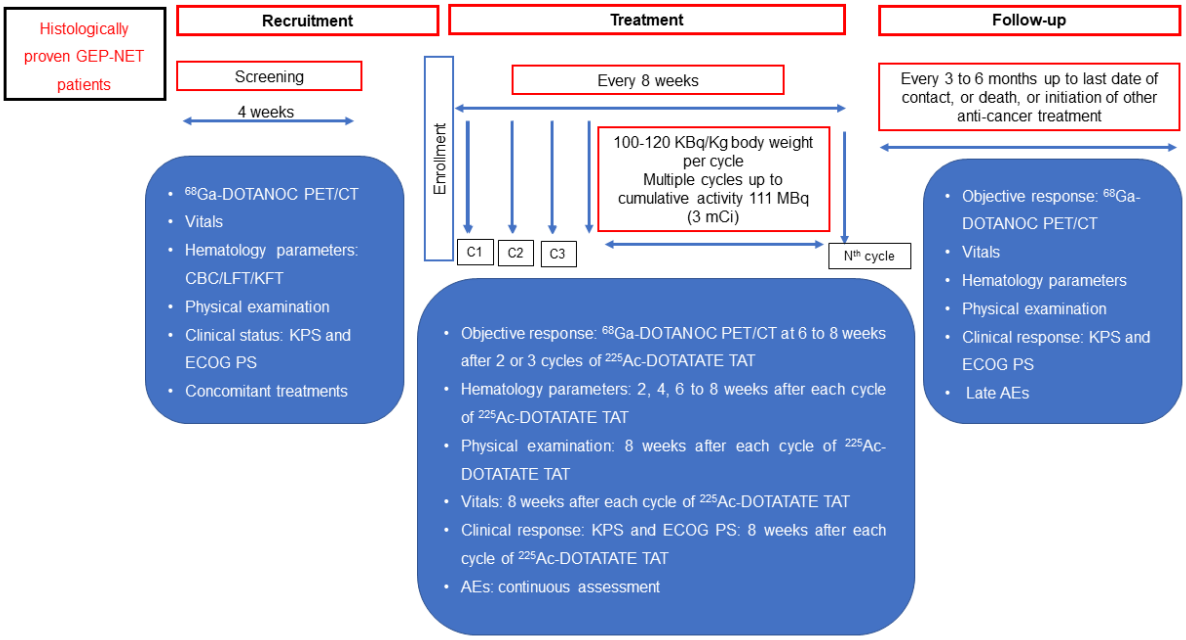

FIGURE 1. ^{225}Ac-DOTATATE TAT treatment regimen and follow-up**.**

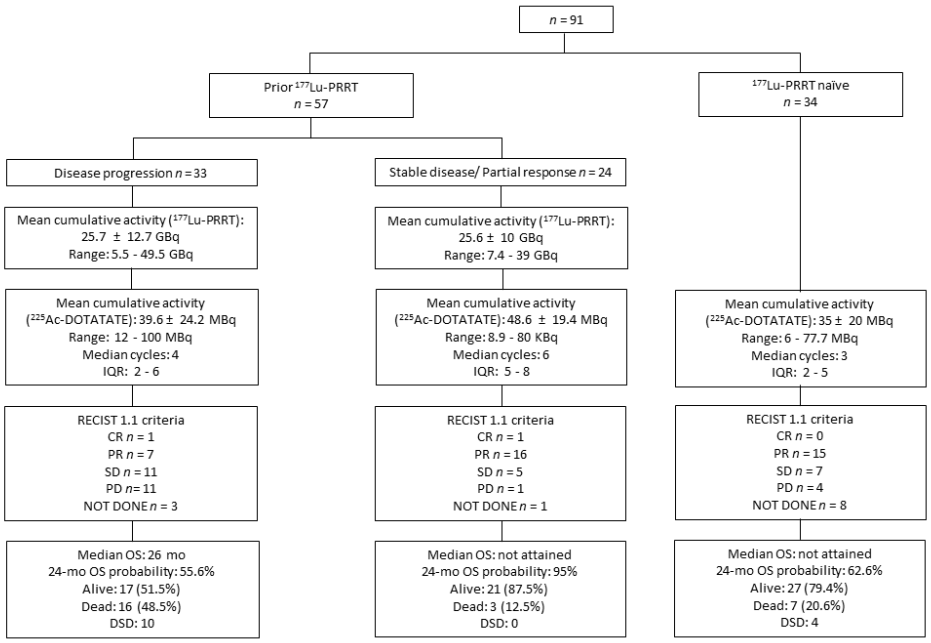

FIGURE 2. Flow chart depicting the treatment details and response in various groups of patients. CR, complete response; IQR, interquartile range; OS, overall survival; PD, progressive disease; PR, partial response; PRRT, peptide receptor radionuclide therapy; RECIST, Response Evaluation Criteria in Solid Tumors (version 1.1); SD, stable disease; TAT, targeted alpha therapy.

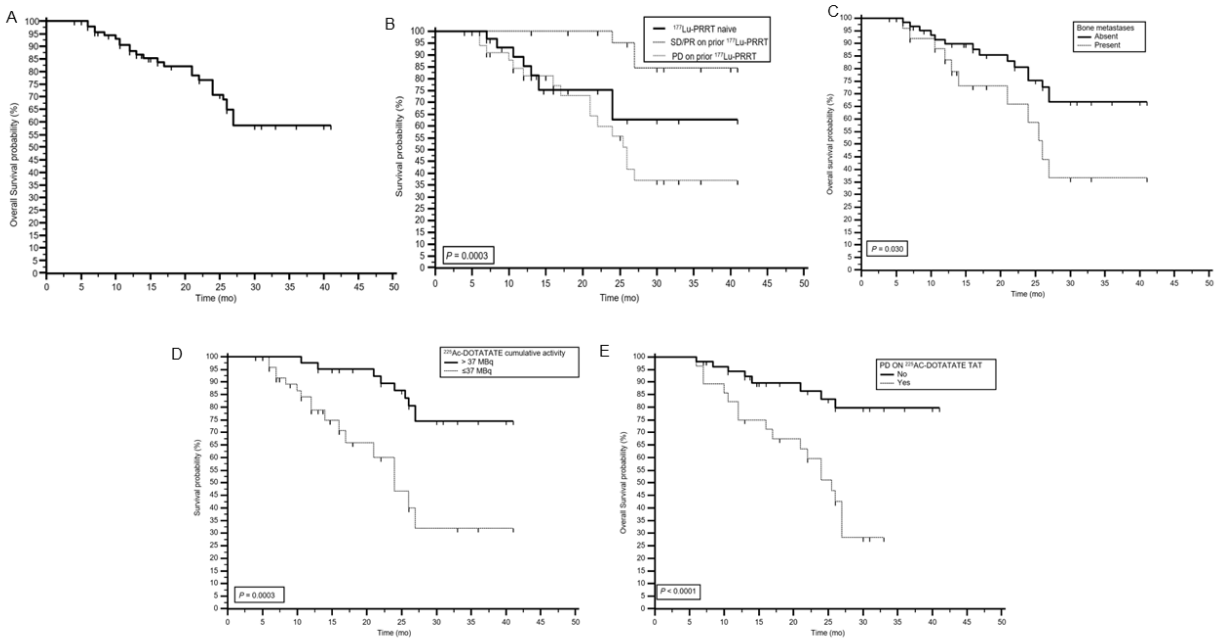

FIGURE 3. Overall survival in (A) the entire patient cohort of 91 patients who had been treated with ^{225}Ac-DOTATATE; (B) based on the disease status on prior Lu-PRRT; (C) presence of bone metastases; (D) according to the cumulative dosage of ^{225}Ac-DOTATATE received; (E) according to the disease status on ^{225}Ac-DOTATATE therapy

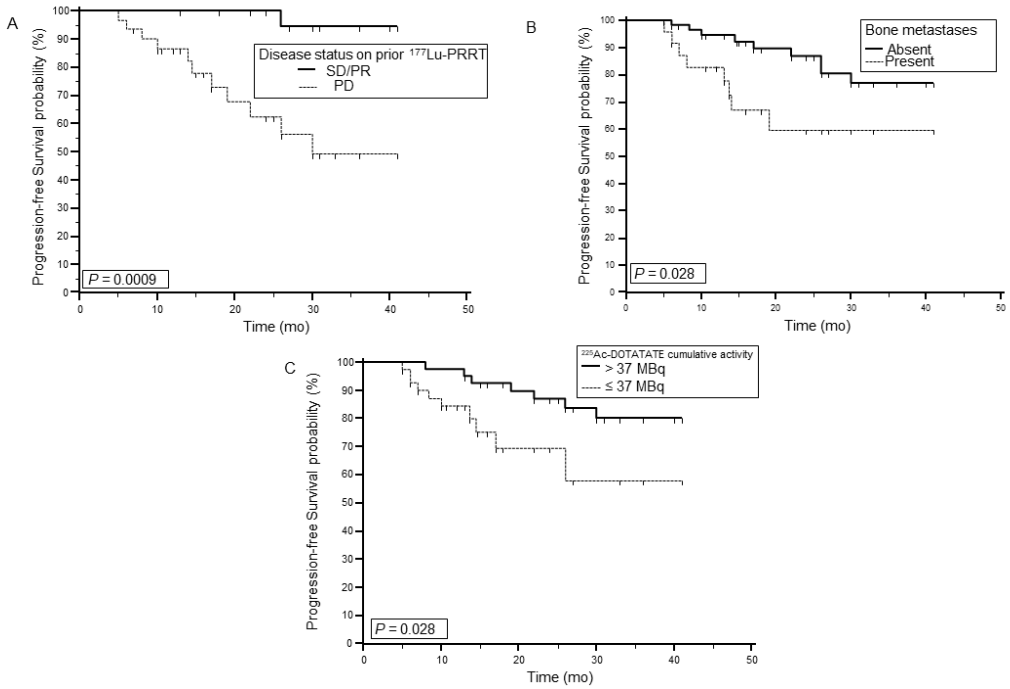

FIGURE 4. Radiological progression-free survival (rPFS) in (A) disease status on prior ^{177}Lu-PRRT, (B) bone metastases patient, and (C) cumulative activity of ^{225}Ac-DOTATATE received. PD, progressive disease; PRRT, peptide receptor radionuclide therapy.

Graphical Abstract

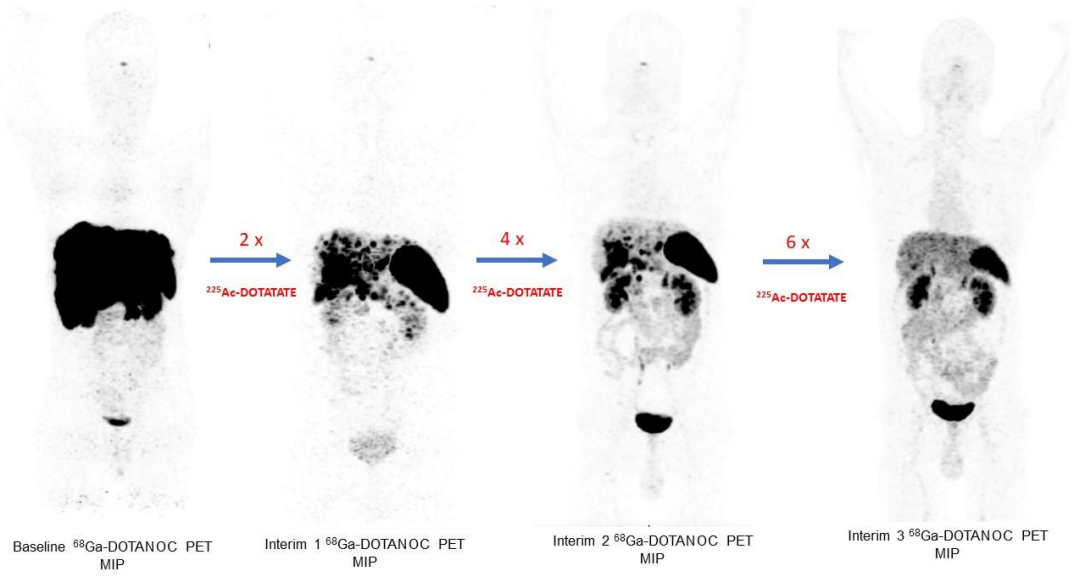

TABLE 1. Patient Characteristics at Baseline (n = 91)

Characteristics	**Value**
Age, mean±SD (range), years	54.3±11.6 (25–75)
Sex	
Male	54 (59.4%)
Female	37 (40.6%)
Tumor location	
Pancreas	30 (33%)
Stomach	7 (7.7%)
Appendix	1 (1%)
Ileum	12 (13%)
Duodenum	13 (14.3%)
Jejunum	2 (2.2.%)
Colon	2 (2.2%)
Rectum	8 (8.8%)
Abdominal NET with unknown primary	16 (17.6%)
WHO Tumor grade (Ki67 tumor proliferation index)	
Grade I (<2%)	33 (36.2%)
Grade II (3–20%)	48 (52.7%)
Grade III (>20%)	7 (7%)
Not accessible	3 (3.3%)
Previous surgery	20 (22%)
Prior chemotherapy	20 (22%)
Prior ^{177}Lu-DOTATATE therapy	57 (62.6%)
ECOG status	
1 to 2	63 (69%)
3 to 4	28 (31%)

NOTE. Data are presented as No. (%) unless otherwise noted.

Abbreviations: NET, neuroendocrine tumor; SD, standard deviation.

TABLE 2. Morphological Tumor Response Based on the Primary Tumor Site

	Prior ^{177}Lu-PRRT (n = 57)						**^{177}Lu-PRRT naïve (n = 34)**				
Site of primary tumor	**CR**	**PR**	**SD**	**PD**	**Not assessed**	**Site of primary tumor**	**CR**	**PR**	**SD**	**PD**	**Not assessed**
Foregut (n = 32)	1 (3%)	13 (40.6%)	10 (31%)	6 (18.7%)	2 (6%)	**Foregut (n = 15)**	0	7 (46.6%)	2 (13.3%)	3 (20%)	3 (20%)
Midgut (n = 11)	0	6 (54.5%)	3 (27.3%)	1 (9%)	1 (9%)	**Midgut (n = 9)**	0	5 (55.6%)	2 (22.2%)	0	2 (22.2%)
Hindgut (n = 7)	1 (14.3%)	2 (28.6%)	2 (28.6%)	2 (28.6%)	0	**Hindgut (n = 1)**	0	0	1 (100%)	0	0
Unknown primary (n = 7)	0	2 (28.6%)	1 (14.3%)	3 (42.8%)	1 (14.3%)	**Unknown primary (n = 9)**	0	3 (33.3%)	2 (22.2%)	1 (%)	3 (33.3%)
Total (n = 57)	2 (3.5%)	23 (40.3 %)	16 (28%)	12 (21%)	4	**Total (n = 34)**	0	15 (44%)	7 (20.6%)	4 (11.8%)	8 (23.6%)

NOTE. Data are presented as No. (%).

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; PRRT, peptide receptor radionuclide therapy; SD, stable disease.

Supplementary Data

Study Description

Brief summary

The aim of this study was to evaluate the long-term outcome of ^{225}Ac-DOTATATE Targeted Alpha Therapy (^{225}Ac-DOTATATE TAT) in Gastroenteropancreatic-Neuroendocrine Tumor (GEP-NET) Patients.

Study Design

Study type: Prospective, single-arm, single center, Interventional Study

Masking: None

Primary purpose: Treatment response

Condition: Gastroenteropancreatic Neuroendocrine tumor Patients

Study Start Date: April 18, 2018

Date of last patient recruitment: October 2021

Last date of follow-up assessment: February 20, 2022

Arms and Interventions

Interventional arm:

^{225}Ac-DOTATATE: Drug: ^{225}Ac-DOTATATE

Peptide receptor radionuclide therapy (PRRT) using ^{225}Ac-DOTATATE 100 - 120 KBq/Kg body weight per cycle [3-3.2 µCi/kg] diluted in 50 mL of saline was administered over 30 minutes (flow rate 1.6 mL/min) every 8 weeks.

Maximum cumulative activity: up to 1,11,000 kBq/111MBq [3 mCi]).

Performed at 8-weekly intervals, through intravenous slow infusion over 30 minutes.

Other: Amino-Acid Solution

For kidney protection, a single-day kidney protection protocol was followed,

- consists of lysine (23.3 g) and arginine (8 g) in 1 L of amino acid mixture in water for injection solution.
- This cocktail was infused over 4 hours, starting 30–60 minutes before the ^{225}Ac-DOTATATE infusion.

Radiosensitizing chemotherapy with capecitabine (1000 mg orally twice daily) was given on days 0–14 of every cycle.

Definitions and Outcome Endpoints.

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), or death due to disease, whichever occurred first.

Outcome Measures

Primary Outcome Measure

Overall Survival (OS)

Definition: Time from the initiation of ^{225}Ac-DOTATATE TAT to the occurrence of death due to any cause or the date of the last contact.

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

Secondary Outcome Measures

1. **Progression-free survival (rPFS)**

Definition: From date of initiation of ^{225}Ac-DOTATATE TAT until the date of first observation of radiographic progression according to RECIST version 1.1 criteria or the development of pleural/pericardial effusion/ malignant ascites, or disease-specific death, whichever occurred first.

- Patients without disease progression were censored at the date of their last evaluable scan,
- Patients with no evaluable scans were censored at the date of randomization

2. **Objective response rates (ORR)**

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

According to RECIST 1.1 criteria, complete response (CR) was a complete resolution of all lesions, partial response (PR) was >30 % decrease in sum of the longest diameters of the target lesion, and >20% increase in the sum of longest diameters of the target lesions was considered progressive disease (PD). Scans demonstrating neither PR nor PD was categorized as stable disease (SD).

Imaging Modality: Diagnostic ^{68}Ga-DOTANOC PET/CT

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

First scan (Baseline scan): Conducted prior to the initiation of ^{225}Ac-DOTATATE therapy.

Follow-up scans: Repeated after every 6–8 weeks after completing every 2–3 cycles of ^{225}Ac-DOTATATE TAT or if the principal investigator suspects clinical disease progression or as per the PIs discretion.

After completion of ^{225}Ac-DOTATATE therapy regimen follow-up scans were performed at every 12 to 24 week intervals, or if any signs of clinical disease progression are observed, or up to the initiation of other anti-cancer treatments.

3. Clinical response

Clinical response assessment was done by the Karnofsky performance status (KPS) and Eastern Cooperative Oncology Group (ECOG) performance status parameters.
KPS ranged from 100 to 0 (100: no evidence of disease and no complaints; 0: dead).

The ECOG status ranged from 0 to 5 (0: fully active, able to carry on all pre-disease performance without restriction and 5: dead).

Time Frame

First time point: Prior to the initiation of ^{225}Ac-DOTATATE therapy

Second time point: At 8 weeks after each cycle of ^{225}Ac-DOTATATE therapy, or study withdrawal, or death.

4. Adverse-event profile

Patients were given a diary in which they could document any side effects or discomfort.

Treatment-related AEs were documented using National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) and The Food and Drug Administration (FDA) document entitled ``Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.[21,22]

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

5. Disease Control Rate

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

Time Frame: From the date of first ^{225}Ac-DOTATATE treatment until date of first documentation of radiographic progression or the date of death due to any cause, whichever occurs earlier.

Eligibility criteria

Inclusion Criteria

- Age more than 18 years and any gender
- Patients with histologically or cytologically confirmed Neuroendocrine tumors from the inoperable or metastatic gastro-entero-pancreatic neuroendocrine tumor site.
- History of prior concomitant therapies, such as SSAs and chemotherapy, as well as ^{177}Lu-DOTATATE therapy.
- At least one measurable lesion on the computed tomography (CT) component of the baseline gallium (^{68}Ga)-DOTANOC positron-emission tomography (PET)/CT scan (uptake ≥liver, or Krenning score ≥3, compared on maximum intensity projection, coronal and transaxial images).
- At least 6 weeks gap from the last ^{177}Lu-DOTATATE therapy
- Patients who did not receive other treatments (e.g. chemo- or radiotherapy) from one month before to two months after the completion of ^{225}Ac-DOTATATE cycles.
- Patients ECOG performance status ≤4
- Patients Karnofskys performance status of ≥40
- Patients with GFR level >40 ml/min/1.73 m^2 BSA
- Heamoglobin ≥ 9 gm/dL
- Platelet count ≥75,000 cells/mm3
- Creatinine ≤ 1.6 mg/dL
- Participant willing to give written informed consent for the participation in the study

Exclusion criteria

- Negative ^{68}Ga-DOTANOC PET/CT scan
- Patients treated with Sandostatin LAR within 4 weeks
- Participation in another clinical trial with any investigational agents within 30 days prior to study screening.
- Uncontrolled hypertension
- Anticipated life expectancy of less than 3 months
- Patients with history of prior cardiac disease
- serum bilirubin >3 mg/dL)
- Karnofsky performance status (KPS) <40
- Active or symptomatic viral hepatitis or chronic liver disease patients
- Acute grade 3 or 4 toxicities of prior therapies
- Patients not giving written informed consent

Dose Modifications

- No dose modifications were implemented.

Reasons for Cessation of Therapy

- Exceptional response during the course of treatment
- Document disease progression
- Death
- Patient's withdrawal of consent for further treatment
- Adverse and serious adverse events related to the treatment
- Lack of adherence to the treatment protocol due to unavoidable pandemic conditions

Statistical Analysis

D'Agostino-Pearson test was used for all data to measure the normality of distribution. Based on the normality of parameters, continuous variables were represented as mean, standard deviation, range, median, and interquartile range (IQR).

Comparisons between parameters of the same population at different timepoints were analyzed using a paired *t*-test (parametric test), or Wilcoxon signed-rank test (non-parametric test).

OS and PFS plots were constructed using the Kaplan-Meier methodology; a log-rank test was used to compare survival between the groups.

A Cox proportional hazards regression was carried out to determine factors associated with OS. P-values<0.05 were considered to be significant.

The analysis was conducted using MedCalc statistical software (version 15.1; MedCalc Software Ltd, Ostend, Belgium).

SUPPLEMENTAL TABLE 1. Site of primary tumor and WHO grade (n = 91)

Primary tumor site	**No. of patients (%)**	**Grade 1**	**Grade 2**	**Grade 3**	**Not assessed**
Pancreas	30 (33%)	11	15	3	1
Stomach	7 (7.7%)	2	4	0	1
Appendix	1 (1%)	0	1	0	0
Ileum	12 (13%)	5	6	0	1
Duodenum	13 (14.3%)	6	5	2	0
Jejunum	2 (22%)	1	1	0	0
Colon	2 (22%)	1	1	0	0
Rectum	8 (8.8%)	3	5	0	0
Abdominal NET with unknown primary	16 (17.6%)	4	10	2	0

NOTE. Data are presented as No. (%) or No.

Abbreviations: NET, neuroendocrine tumor; WHO, World Health Organization

SUPPLEMENTAL TABLE 2. Extent of Metastases on Baseline ^{68}Ga-DOTANOC PET/CT scan

Location	**No. of patients (%)**
Primary	55 (60.4%)
Lymph node	66 (72.5%)
Liver	88 (96.7%)
Bone	25 (27.5%)
Lungs	6 (6.6%)
Brain	2 (2.2%)
Adrenal	6 (6.6%)
Other sites	
Mesentery	1 (1%)
Brain	2 (2.2%)
Ovaries	1 (1%)
Kidneys	1 (1%)
Serosal deposit	1 (1%)
Duodenum Marrow	2 (2.2%) 1 (1%)

NOTE. Data are presented as No. (%).

SUPPLEMENTAL TABLE 3. Prior treatment before study entry

Treatment	**No. of patients (%)**
Previous surgery	21 (23%)
Surgery of primary tumor	16 (17.6%)
Metastasectomy	5 (5.5%)
Prior octreotide	70(77%)
Short acting	1 (1%)
Long acting	69 (76%)
Ongoing octreotide	10 (11%)
Prior chemotherapy	18 (20%)
Cisplatin + etoposide	6 (33.3%)
Capecitabine + temozolomide	3 (16.6%)
Sunitinib	3 (16.6%)
Carboplatin only	2 (11.1%)
Gemcitabine + oxaliplatin	2 (11.1%)
Cisplatin+carboplatin	1 (5.5%)
Sorafenib	1 (5.5%)
Everolimus	6 (6.6%)
Prior ^{177}Lu-DOTATATE therapy	57 (62.6%)
Disease status on previous ^{177}Lu-DOTATATE PRRT	n = 57
Progressive disease	33(58%)
Stable disease	24 (42%)
Median No. of ^{177}Lu-DOTATATE cycles (range)	6 (1–7)

NOTE. Data are presented as number (No.) (%) un less otherwise noted.

Abbreviations: mTOR, mammalian target of rapamycin; PRRT, peptide receptor radionuclide therapy.

SUPPLEMENTAL TABLE 4. Details of number of ^{225}Ac-DOTATATE therapy cycles

Number of cycles	**Number of patients**	**Total number of cycles**
1	3	3
2	13	26
3	16	48
4	15	60
5	7	35
6	11	66
7	9	63
8	5	40
9	8	72
10	4	40
Overall	**91**	**453**

SUPPLEMENTAL TABLE 5. Details of disease status on RECIST 1.1 criteria in 26 deceased patients

n =14 PD	n = 12
	CR on TAT (n = 1) Died due to adenocarcinoma of lung (dual malignancy)
	PR on TAT (n = 3)
	COVID-19 followed by uncontrolled DM2 (n = 1)
	Immunotherapy related toxicity (n = 1)
	Cause of death not known (n = 1)
	SD ON TAT (n = 4)
	COVID-19 related death (n = 1)
	Cause of death not known (n = 3)
	RECIST 1.1 not assessed (n = 4)
	Death due to toxicity from immunotherapy (n = 1)
	Death due to ca gall bladder (dual malignancy) (n = 1)
	Cause of death not known (n = 2)

TAT, targeted alpha therapy

SUPPLEMENTAL TABLE 6. Comparison between disease control group on prior ^{177}Lu-PRRT versus the ^{177}Lu-PRRT naïve group.

Variables	**SD/PR on prior ^{177}Lu-PRRT group (n = 24)**	**Prior PRRT naïve group (n = 34)**	**P=value**
Age (mean ± SD)	54.6 ± 10.2	56.8 ± 13.5	0.580
Gender Male/female	12/12	20/14	0.678
WHO tumor grade			
I	11	13	0.867
II/III	12	21	
ECOG status			
1 to 2	18	24	0.942
3 to 4	6	10	
Chemotherapy			
Yes	4	8	0.531
No	21	26	
Bone metastases			
Present	3	11	0.120
Absent	21	23	

SUPPLEMENTAL TABLE 7. Univariate and multivariate Cox proportional hazards regression of predictive and prognostic factors associated with overall survival.

	Univariate analysis			Multivariate analysis	
Parameters	**Median OS (months)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**
Age (years)					
≤54	NA	0.679	0.851 (0.391 - 1.854)		
>54	NA				
Sex					
Male	NA	0.045	0.459 (0.211 - 1.000)		
Female	27				
Distant metastases					
Present	NA	0.199	NE		
Absent	NA				
Bone metastases					
Present	26	0.030	2.277 (0.930 - 5.577)	0.032	2.501 (1.826 – 5.791)
Absent	NA				
Chemotherapy					
No	NA	0.257	1.661 (0.630 - 4.066)		
Yes	26				
WHO tumor grade					
I	NA	0.578	0.861 (0.327 - 1.026)		
II/III	NA				
Previous surgery					
Yes	NA	0.883	0.921 (0.362 - 2.405)		
No	NA				

Previous octreotide					
Yes	NA	0.217	0.573 (0.193 - 1.699)		
No	25.5				
ECOG status					
1 to 2	NA	0.095	1.902 (0.806 - 4.485)		
3 to 4	27				
Prior ^{177}Lu-DOTATATE PRRT					
Yes	NA	0.642	0.820 (0.330 - 2.034)		
No	NA				
Disease status on prior ^{177}Lu-DOTATATE PRRT					
PD	27	0.031	1.900 (0.772 - 4.676)		
SD/PR	NA				
Cumulative activity of ^{225}Ac-DOTATATE					
≤37 MBq	24	0.0003	3.733 (1.654 - 8.428)		
>37 MBq	NA				
Disease progression on ^{225}Ac-DOTATATE therapy					
Yes	21	<0.0001	7.051 (2.372 - 20.955)	<0.0001	8.781 (3.843 - 20.062)
No	NA				

Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; HR, hazard ratio; MR, minimal response; NA, not attained; NCR, near complete response; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response; PRRT, peptide receptor radionuclide therapy; RECIST, Response Evaluation Criteria in Solid Tumors (version 1.1); SD, stable disease; WHO, World Health Organization.

SUPPLEMENTAL TABLE 8. Univariate and multivariate Cox proportional hazards regression of predictive and prognostic factors associated with progression-free survival.

		Univariate analysis		Multivariate analysis	
Parameters	**Median OS (months)**	**P-value (log-rank)**	**HR (95% CI)**	**P-value**	**HR (95% CI)**
Age (years)					
≤54	NA	0.603	1.299 (0.495 - 3.410)		
>54	NA				
Sex					
Male	NA	0.672	0.815 (0.311 - 2.135)		
Female	NA				
Bone metastases					
Present	NA	0.028	2.760 (0.912 - 8.356)		
Absent	NA				
Chemotherapy					
No	NA	0.7066	0.788 (0.247 - 2.512)		
Yes	NA				
WHO tumor grade					
I	NA	0.956	NE		
II	NA				
III	NA				
Previous surgery					
Yes	NA	0.577	0.648 (0.287 - 1.689)		

No	NA				
Previous octreotide					
Yes	NA	0.102	0.432 (0.116 - 1.625)		
No	NA				
Prior ^{177}Lu-DOTATATE PRRT					
Yes	NA	0.0807	NE		
No	NA				
Disease status on prior ^{177}Lu-DOTATATE PRRT					
PD	30	0.0009	13.553 (4.343 - 42.271)	0.011	14.338 (1.853 - 97.698)
SD/PR	NA				
Cumulative activity of ^{225}Ac-DOTATATE					
≤37 MBq	NA	0.028	2.718 (0.999 - 7.393)		
>37 MBq	NA				

Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; HR, hazard ratio; MR, minimal response; NA, not attained; NCR, near complete response; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response; PRRT, peptide receptor radionuclide therapy; RECIST, Response Evaluation Criteria in Solid Tumors (version 1.1); SD, stable disease; WHO, World Health Organization.

SUPPLEMENTAL TABLE 9. Summary of Adverse Events According to Common Terminology Criteria for Adverse Events (Version 5.0).

	Baseline						End of Assessment				
Event	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**		**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Haemoglobin	36	50	0	0	0		32	19	0	0	0
Platelet	19	0	0	0	0		16	0	1	0	0
WBC	16	1	0	0	0		5	0	0	0	0
Creatinine	16	1	0	0	0		11	0	0	0	0
Urea	18	13	12	0	0		21	9	16	0	0
Total bilirubin	7	3	0	0	0		2	3	0	0	0
AST	35	1	1	0	0		38	1	0	0	0
ALT	29	1	0	0	0		21	0	0	0	0
ALP	31	14	5	0	0		32	4	1	0	0
Nausea	3	35	6	0	0		14	14	0	0	0
Gastritis	10	34	2	0	0		20	18	2	0	0
Vomiting	11	8	2	0	0		8	3	0	0	0
Abdominal pain	7	24	7	0	0		18	3	11	0	0
Diarrhoea	4	17	4	0	0		11	2	0	0	0
Abdominal distension	3	13	4	0	0		1	12	8	0	0
Fatigue	5	43	12	0	0		29	8	13	0	0
Loss of appetite	8	43	12	0	0		28	12	11	0	0
Headache	1	8	0	0	0		4	2	1	0	0
Dizziness	1	2	0	0	0		2	0	0	0	0
Flushing	0	5	3	0	0		5	0	0	0	0
Myalgia	16	29	11	0	0		25	12	6	0	0
Malignant ascites	5	3	0	0	0		0	4	0	0	10
Pleural effusion	0	0	0	0	0		0	0	1	0	1

Abbreviations: WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine transferase; ALP, alkaline phosphatase.