Original Article

# Outcome of $^{177}$Lu-DOTATATE Peptide Receptor Radionuclide Therapy in Progressive Metastatic Neuroendocrine Tumors from a Tertiary Care Center

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## Abstract

**Introduction:** Functioning neuroendocrine tumors (NETs) that do not respond to standard therapies are commonly considered for Peptide Receptor Radionuclide Therapy (PRRT). The benefit of $^{177}$Lu-DOTATATE PRRT in patients with progressive metastatic NET was analyzed and survival in multi-organ involvement. **Methods:** Forty-one patients with refractory, progressive, or advanced symptomatic NETs, with or without previous treatment modalities were studied. They were treated with $^{177}$Lu-DOTATATE IV infusion 150 mCi per dose up to four cycles. Retrospectively, they were assessed for response to PRRT based on clinical, Imaging-Contrast CT/$^{68}$Ga-DOTATATE PET-CT, and biochemical markers. After treatment, classification based on disease status, symptomatic improvement, and response to treatment based on Chromogranin A level was done. The organs involved and their respective survival benefits, as estimated by Kaplan Meier, were plotted for 60 months. **Results:** The mean serum Chromogranin A level at baseline was 2841 U/ml (Median = 3150). The main site of primary NET was in the pancreas, and the most common site for metastases was the liver. Following PRRT, all patients, except one, reported an improvement in their baseline complaints. Most (82%) reported no new symptoms, and 50% had a reduction in serum Chromogranin A levels. Follow-up imaging showed regression in one patient, static tumor in 18, and progression in rest. Considering radiological and clinical responses, the overall benefit was noticed in 29 (70%) patients. Despite symptomatic improvement, there was no significant survival benefit for those with pancreatic, liver, or nodal metastasis. **Conclusion:** A majority of patients who were treated with PRRT demonstrated clinical, radiological as well as biochemical positive responses warranting an earlier consideration for this well-tolerated treatment modality.

**Keywords:** $^{68}$Ga-dotatate, Kaplan–Meier survival estimates, $^{177}$Lu-dotatate, NET, neuroendocrine tumor, peptide receptor radionuclide therapy, PRRT

## Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of tumors, ranging from the well-differentiated to poorly differentiated with varying mitotic indexes on which treatment is planned. Although a rare tumor, NETs have been increasingly diagnosed in the last two decades, probably due to greater awareness and better diagnostic methods. At an early stage, many are operable, and hence a complete cure is plausible. These tumors are most often slow-growing in nature and thus are overlooked due to their asymptomatic or mildly symptomatic nature.

When symptomatic, almost half of the patients with NETs have metastases at the time of presentation. The morphological differentiation and Ki-67 mitotic index are used to prognosticate as well as to plan for a holistic approach in the management of patients with neuroendocrine malignancy.[1]

The common primary sites of NETs[2] are the pancreas, the small intestine – jejunum/ileum/duodenum (in descending order), stomach, lung, and the large intestine - appendix,

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caecum, colon, and rectum, with metastases to the liver as the preferential site.

As most NETs are functional, their symptoms are due to the biologically active substances secreted by the tumor *per se*. This results in the development of characteristic clinical syndromes, about the functioning nature of these tumors.

The tumor marker, serum Chromogranin A (Cg A), is most commonly used in the diagnosis, evaluation of the response to treatment, prognosis, and follow-up of patients with NETs. An elevated serum Cg A level is noted in patients with different types of endocrine tumors as well as in certain non-malignant conditions like atrophic gastritis.[3] Further, elevated levels of Cg A are also noted with the use of medications[2] like proton pump inhibitors, antacids, and oral steroids.

In patients with advanced NET, therapies like de-bulking of the primary tumor, chemotherapy, radiotherapy, octreotide, targeted therapy with kinase inhibitors like Everolimus, and peptide receptor radionuclide therapy (PRRT) are used.[4] The response rates of each of these modalities of treatment are highly variable across the globe.[5] PRRT is a targeted therapy for somatostatin receptor-expressing NETs, which are well-tolerated with favorable outcomes.

PRRT is generally considered as a treatment option[6] in the following patients:

1-After debulking the primary lesion;

2-Those with in-operable tumors,

3-Post octreotide;

4-Rarely when there is a contraindication for the above treatment option.[7]

Our study aimed to evaluate the usefulness and effectiveness of PRRT in patients with metastatic NETs in relation to symptom relief, imaging characteristics, and tumor markers.

## Materials and Methods

All patients with symptomatic and/or progressive NETs, and treated with PRRT were included in the study as shown in Table 1 which details the inclusion and exclusion criteria that were used to screen the patients enrolled to build the database. To prevent any loss of data all patients who were treated with PRRT were selected for a period of four years from January 2014 to December 2018 which would allow us to follow them up for at least the subsequent three years [Figure 1]. For these patients to be accepted for PRRT, they need to have histopathological basis of diagnosis with avidity on $^{68}$Ga-DOTATATE PET-CT scan with a performance status of ECOG 1-3 at least. Any patient not fitting into the above criteria was excluded from the study.

### PRRT protocol

The Multidisciplinary Tumor Board of our Institution recommends PRRT after reviewing the $^{68}$Ga-DOTATATE PETCT imaging, the history of the patient, and previous treatments received. The criterion for PRRT is uptake based on $^{68}$Ga-DOTATATE PETCT imaging. The uptake should be at least grade 2 absorption according to Krenning's score. A total of four doses are planned, with the response assessment timed with the number of cycles and clinical improvement. The nuclear medicine physician explains the procedure, costs, risks, and benefits to the patient and their relatives. After the patient gives consent for the same, blood tests and renal scans are done to check the fitness of the patient for PRRT.

Inpatient procedure: A measured dose of $^{177}$Lu-DOTATATE is diluted in saline and loaded in a 50 ml syringe pump with lead barrier protection.[4]

Premedication with anti-emetics, followed by intravenous amino acid solution (2000 ml) for renal protection, is given. After 250 ml of amino acid solution is administered, $^{177}$Lu-DOTATATE is initiated using a syringe pump in a parallel line. A fixed dose of 150 mCi per treatment is administered in each cycle of treatment.

The $^{177}$Lu-DOTATATE IV infusion is started slowly and the patient is monitored. Generally, this is very well tolerated; the few patients, who are nauseous due to the amino acid infusion, are usually managed with conservative measures.

Subsequently, if no untoward effects are noted, the rate of $^{177}$Lu-DOTATATE IV rate is increased. The infusion rate is slowed down if the patient is nauseous or uncomfortable. Usually, the administration of $^{177}$Lu- DOTATATE is completed within 30 to 40 minutes.

The amino acid solution infusion will last for a total of four hours. Patients naive to PRRT are observed for 24 hours. For the subsequent three doses, they are discharged immediately after therapy, if asymptomatic. Radioactivity is measured before discharge to certify that the patient is "safe for discharge" as per the AERB norms (Less than 50 mSv).

**Table 1: Details of inclusion and exclusion criteria used in this study**

| Inclusion criteria | Exclusion criteria |
|---|---|
| Patients with locally inoperable, metastatic, and progressive NETs | Patients with poorly differentiated NETs |
| Histopathological confirmed well-differentiated, intermediate NETs | Non-avid disease (less than Liver) on $^{68}$Ga-DOTATATE PET-CT |
| Avid disease (equal or greater than Liver) on $^{68}$Ga-DOTATATE PET-CT | Inadequate laboratory parameters at baseline- Hemoglobin <80 g/L, platelet count <75 g/L, ALT/AST >3 times upper range of normal, eGFR <45 ml/min |
| Treated with a minimum of 4 cycles of PRRT followed up to 36 months | Insufficient follow-up period: <36 months |
| ECOG 1–3 | ECOG equal to 4 |

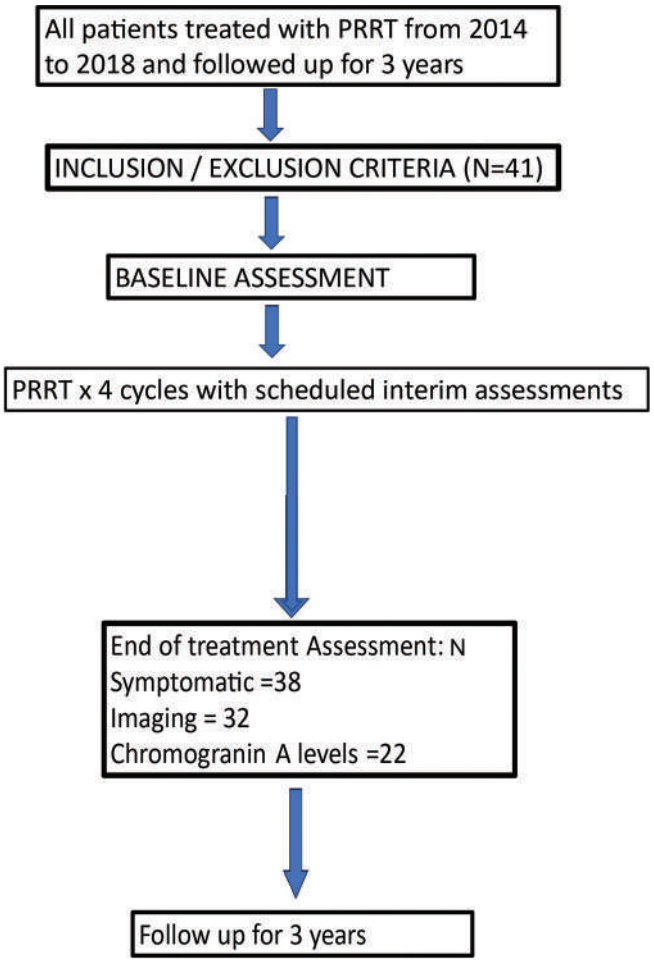


**Figure 1:** Flow chart diagram showing study overview

Clinical evaluation: For the patients in this study, baseline assessment of symptoms (pain, fatigue, nausea, loss of appetite, breathlessness, loose stools, Anxiety), were monitored and noted at each intervention, after treatment, and during follow-up.

Symptoms assessment was done by open-ended questions with the patient being encouraged to tell all complaints and then describe their severity. The list was completed by confirmation of the absence of other symptoms.

Biochemical data: The levels of Chromogranin A which is an acidic soluble glycoprotein located within neurosecretory granules secreted by neuroendocrine tumor cells are measured by a blood serum test. Chromogranin A assay was done by sandwich immunoassay using Time-Resolved Amplified Cryptate Emission (TRACE) technology (ThermoFisher Brahms, Hennigsdorf, Germany) with the 29-min Kryptor assay. Baseline serum Chromogranin A levels and follow-u*P* values after 3-4 cycles of PRRT were also recorded.

Imaging: All patients underwent a 68 Ga-DOTATATE PET-CT at three weeks before starting the treatment and again at 12 weeks, after 4 cycles of PRRT with $^{177}$Lu therapy.

A combination of radiological (contrast CT), clinical, and biochemical criteria was used for the response evaluation. Both functional and anatomic imaging were considered for the combined imaging response. This was done by an experienced Radiologist, in conjunction with two Nuclear Medicine physicians, and a consensus was obtained to conclude.

## Follow-up for further treatments

The subsequent PRRT treatments were given at eight weeks from the last dose. At this time, in consultation with the medical oncologist, other treatments with octreotide and Everolimus were also continued.

Subsequent PRRT doses were deferred if there was a deterioration in the patient's condition due to the progression of the disease or if contraindicated due to other medical co-morbidities. Such patients were advised to consider treatment options with other lines of chemotherapy under the supervision of medical oncology.

## Analysis

$^{68}$Gallium tagged-DOTATATE PET CT imaging, biochemical tumor markers with serum Chromogranin A levels, and clinical symptomatic evaluation were performed at baseline as well as on follow-up after PRRT.

This is a retrospective study and Symptomatic assessment was done only from the perspective of clinician. The complaints of the patient were asked and severity noted as expressed by the patient. There was no objective measurement tool used to categorize these symptoms or grade them.

The biochemical response was based on the change in biochemical markers (Calcitonin level, Chromogranin A level, CEA, 5HIAA, Gastrin, etc.) categorized into an increase from baseline, stable, or decreased from the baseline level.

Imaging response was based on combined reporting by Radiologist and Nuclear Medicine physician after reviewing Contrast CT/$^{68}$Ga-DOTATATE PET-CT using RECIST 1.1 criteria; along with the metabolic activity viewed in the PET images.

RECIST 1.1 criteria[8] are used to assess if there is complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).

## Progressive disease (PD)

The ≥20% increase in the sum of diameters of target lesions, taking as reference the smallest sum in the study, is called the Nadir. This includes the baseline sum if that is the smallest on the study.

In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

The appearance of one or more new lesions is always considered progression.

Unequivocal progression of non-target lesions is also considered a progression.

### Stable disease (SD)

Neither sufficient shrinkage to qualify for a partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum of length diameters (SLD) while in the study.

### Partial response (PR)

At least a 30% decrease in the sum of length diameters (SLD) of target lesions, as compared to baseline sum diameters.

### Complete response (CR)

Disappearance of all target and nontarget lesions.

Any pathological lymph nodes must have a reduction in the short axis to <10 mm.

### Statistical analysis

The data was analyzed using SPSS 21.0. All study variables were summarized using descriptive statistical methods. Numerical variables were described using means with standard deviations if normally distributed; and medians with interquartile ranges for non-normally distributed variables. Categorical variables were summarized using frequencies with percentages.

The association between survival status and other covariates was assessed using Chi-square tests. Kaplan–Meier analysis was performed to examine the time to death. All analysis was performed STATA (Statacorp, College Station, Texas, USA).

### Ethical aspects

This was a retrospective study carried out in the nuclear medicine department of a tertiary care center in South India. The study was approved by the Institutional Review Board (IRB Min No. 13219 Retro dated 22.07.2020).

Written informed consent was not obtained as it was a retrospective study and was cleared by IRB for use of the patient data for research and educational purposes. The study was conducted following the principles of Declaration of Helsinki.

## Results

The total number of patients found eligible for the study, and whose results were analyzed was 41. In our study, the mean cumulative dose of $^{177}$Lu-DOTATATE was 451 mCi (SD = 158. Range: 117–673 mCi), which spread over a mean of 3 cycles (SD = 1. Range: 2–4 cycles).

The mean age of the patients was 46 ± 13 years (range: 21–75 years). The median age was 45 (IQR: 35–55 years). Males constituted 71% of them.

The parameters of data that were built into the database collected from the patients were the primary site of tumor, treatment already received, the line of treatment, histopathology report, MIB 1 index or grade of tumor, number of sites of the tumor, organs which were involved, age of the patient, gender, BMI, co-morbid conditions, the total dose received, the number of fractions received, the biochemical markers (Calcitonin level, Chromogranin A level, CEA, etc.), imaging reports based on RECIST criteria, symptoms (pain, fatigue, nausea, loss of appetite, breathlessness, loose stools, anxiety) number of months after the last fraction of PRRT, Months to Subsequent therapy/progression/death, Overall survival duration and progression-free survival interval.

Table 2 shows these baseline parameters and the respective age, along with the comorbidities.There was fair distribution among all ages and across a wide range of BMI. No association of BMI with any comorbidity was noted. The patient's tumor profile and the treatment offered were fairly distributed.

Most of the primary lesions were in the pancreas, followed by the small bowel. The most common site of distant metastases was the liver. Surgical intervention was done in 42% of the patients. Twenty patients had undergone multiple modalities of treatment before PRRT.

Statistical analysis was done using SPSS to calculate the *P* value to determine if there is any significance in the observed difference between the groups compared and thus check for any association with mortality in the following categories [Table 3].

The median age and mortality did not show any significant association (*P* value = 0.448) neither did the gender of the patient (*P* value = 0.251).

Involvement of lung (*P* value = 0.305), liver (*P* value = 0.368), bone (*P* value = 0.388), or pancreas (*P* value = 0.199), and mortality did not show any significant association.

There was also no significant association between nodal involvement and mortality. (*P* value = 0.495).

Statistical analysis was done using SPSS to calculate the *P* value to determine if there is any significance in the difference between groups compared and thus for any association with mortality and Serum Chromogranin A levels in the following categories [Table 4].

Serum Chromogranin A levels for all patients at baseline (pre-treatment (*P* value = .605)) and following intervention (Post-treatment (*P* value = 0.277)) did not show any significant association. The fall in the serum chromogranin A levels as a response to PRRT was also evaluated as a marker of response (delta chromogranin %) but did not show any significant association (*P* value = 0.385).

Serum Chromogranin A levels for patients with liver involvement at baseline (pretreatment (*P* value = 0.602)) and following intervention (post-treatment (*P* value = 0.460)) did not show any significant association. The fall in the serum Chromogranin A levels as a response to PRRT [Figure 2] was also evaluated as a marker of response (Delta

**Table 2: Baseline characteristics of patients**

| Characteristic | Quantity Number (%) |
|---|---|
| [A] Site of primary tumor | |
| 1-Pancreas | 12 (29.3) |
| 2-Small bowel | 12 (29.3) |
| 3-Lung | 7 (17.1) |
| 4-Thymus | 4 (9.8) |
| 5-Thyroid | 3 (7.3) |
| 6-Others | 3 (7.3) |
| 7-Above diaphragm | 16 (39) |
| 8-Below diaphragm | 25 (61) |
| [B] PRRT Line of treatment | |
| a-1st line | 16 (39) |
| b-2nd line | 11 (26.8) |
| c-3rd line | 12 (29.3) |
| d-4th line | 2 (4.9) |
| [C] Diagnosis | |
| 1- NET: Pancreas=12 Bowel=11 Others=4 | 27 (65.9) |
| 2-Carcinoid | 8 (19.5) |
| 3-Medullary thyroid cancer | 3 (7.3) |
| 4-Paraganglioma | 1 (2.4) |
| 5-Thymic tumor | 2 (4.9) |
| [D] Metastatic sites at baseline | |
| 1-Liver | 28 |
| 2-Lung | 13 |
| 3-Nodes | 22 |
| 4-Bones | 6 |
| 5-Others | 5 |
| [E] Prior Treatment | |
| 1-Octreotide | 10 |
| 2-Chemotherapy [*] | 9 |
| 3-Targeted therapy | 3 |
| 4-Surgery | 18 |
| 5-MIBG therapy | 3 |
| 6-Multiple therapies | 20 |
| [F] Comorbidities | |
| 1-DM | 4 |
| 2-HT | 7 |
| 3-Hypothyroid | 5 |

| [G] Character ($n=35$)† | BMI Group | | | Age Group | | | |
|---|---|---|---|---|---|---|---|
| | BMI <21 ($n=15$) | BMI 21–25 ($n=15$) | BMI >25.0 ($n=5$) | ≤40 ($n=12$) | 41–50 ($n=9$) | 51–60 ($n=10$) | >60 ($n=4$) |
| Male (27) | 12 | 12 | 3 | 9 | 5 | 9 | 4 |
| Female (8) | 3 | 3 | 2 | 3 | 4 | 1 | 0 |
| DM (4) | 2 | 2 | 0 | 1 | 0 | 3 | 0 |
| HT (7) | 2 | 3 | 2 | 1 | 1 | 4 | 1 |
| Hypothyroid (5) | 2 | 2 | 1 | 3 | 1 | 1 | 0 |

*Chemotherapy agents used were Platinum based (Cisplatin or Carboplatin), Etoposide, Capecitabine, Temozolomide, and Gemcitabine. †Data for 6 patients missing

Chromogranin %) but did not show any significant association ($P$ value = 0.409).

Serum chromogranin A levels for patients with nodal involvement at baseline (pre-treatment ($P$ value = 0.739)) and following intervention (post-treatment ($P$ value = 0.754)) did not show any significant association. The fall in the serum Chromogranin A levels as a response to PRRT was also evaluated as a marker of response (delta chromogranin %) but did not show any significant association ($P$ value = 0.917).

**Table 3: Association of metastatic site and gender with mortality**

| | | Alive ($n$=15) | Dead ($n$=26) | $P$ |
|---|---|---|---|---|
| Age (median) | | 41 | 45 | 0.448 |
| Gender | Male | 9 (31.0%) | 20 (69.0%) | 0.251 |
| | Female | 6 (50.0%) | 6 (50.0%) | |
| Lung | Not affected | 12 (42.9%) | 16 (57.14%) | 0.305 |
| | Involved | 3 (23.1%) | 10 (76.9%) | |
| Liver | Not affected | 6 (46.2%) | 7 (53.8%) | 0.368 |
| | Involved | 9 (32.1%) | 19 (67.9%) | |
| Bone | Not affected | 14 (40%) | 21 (60%) | 0.388 |
| | Involved | 1 (16.7%) | 5 (83.3%) | |
| Pancreas | Not affected | 8 (29.6%) | 19 (70.4%) | 0.199 |
| | Involved | 7 (50.0%) | 7 (50.0%) | |
| Node | Not affected | 8 (42.1%) | 11 (57.9%) | 0.495 |
| | Involved | 7 (31.8%) | 15 (68.2%) | |

**Table 4: Association of chromogranin a level (NG/ML) with mortality**

| | Alive | Dead | $P$ |
|---|---|---|---|
| All patients | | | |
| Chromogranin A Pre | 6126 (15322) ($n$=9) | 768 (1543) ($n$=19) | 0.605 |
| Chromogranin A Post | 4123.32 (10340) ($n$=8) | 690.15 (1126) ($n$=13) | 0.277 |
| Delta chromogranin % | −256.56% (498.07) | −45.85% (192.62) | 0.385 |
| Liver involved | | | |
| Chromogranin A Pre | 7859 (17241) | 919 (1743) | 0.602 |
| Chromogranin A Post | 5439 (11890) | 809 (1298) | 0.460 |
| Delta chromogranin % | −42.55% (41.22) | −157.17% (450.77) | 0.409 |
| Node involved | | | |
| Chromogranin A Pre | 9507 (20697) | 1288 (2106) | 0.739 |
| Chromogranin A Post | 6117 (13162) | 1128 (1572) | 0.754 |
| Delta chromogranin % | −76.74% (233) | −318% (599) | 0.917 |

Table 4 shows the association of Serum Chromogranin A levels with mortality.

Independent T-Test for two independent means to evaluate whether nodal disease was associated with increased Chromogranin A values showed no significant effect; $t(26) = 1.04$, $P = 0.15$.

There was no significant association between serum Chromogranin A levels and survival. There was also no significant association found with affected organs and serum Chromogranin A levels as well. There was no statistically significant association between the organ involved and mortality. This is because the power of the study is limited by the small number of patients in each category.

Considering all the values Chromogranin A assay, the mean is 2,433.91 with a standard deviation of 4,413.19. The coefficient of variation (CV) would be (Standard Deviation/Mean) × 100% = (4,413.19/2,433.91) × 100% =181.4%.

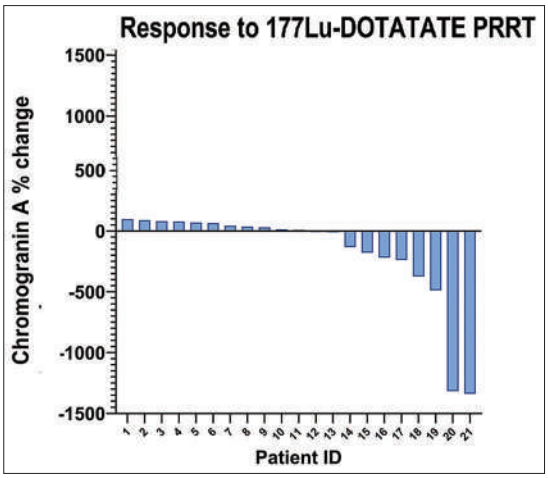


**Figure 2:** Change in chromogranin-A level in response to PRRT is shown as a Waterfall plot. Y-axis showing the percentage change in chromogranin levels post PRRT (some patients showed increased levels – progression, while others showed decreased levels - Regression), and the X-axis represents the patients

This indicates that the data has a high degree of variability compared to the mean.

The patients were also analyzed by treatment outcomes [Table 5]. Secondary analysis to identify variables that can help us predict responders as opposed to nonresponders was not done.

Most of the patients were found to have benefited from PRRT. The greatest benefit was in the symptomatic response with modest benefit, as analyzed by biochemical and imaging response evaluation.

The survival benefits of these patients after the end of treatment were evaluated using the Kaplan–Meier Survival curve [Figure 3]. There was no significant difference in survival between those with or without hepatic metastasis. The same was true for other organ involvements (pancreas, lung, nodes) as well.

The utility of the $^{68}$Ga- DOTATATE PET CT study in a patient at baseline, before the individual intervention, and response to it after the intervention is noted in Figures 3-5.

The survival benefits of these patients after the end of treatment were evaluated using the Kaplan–Meier Survival curve. There was no significant difference between those with or without hepatic metastasis. When we consider the involvement of other organs (pancreas, lungs, nodes) likewise there is no difference seen in the survival benefit between those affected by the disease and those not affected. Overall survival is favorable if tumor was situated below the diaphragm [Figure 6]. Progression free survival also showed a similar trend [Figure 7].

## Discussion

Neuroendocrine Tumors are a mixed group of uncommon malignancies. They are now being increasingly diagnosed

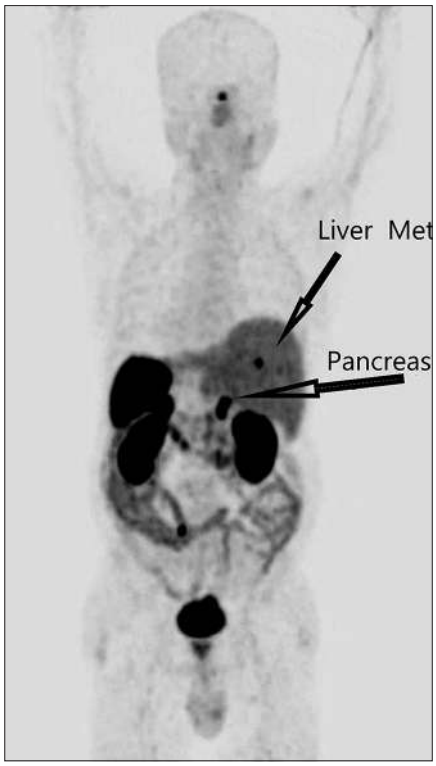


**Figure 3:** $^{68}$Ga- DOTATATE PET CT study of a 57-year-old gentleman who was diagnosed to have metastatic NET at baseline scan with uptake in segment 7 of liver and tail of pancreas as possible primary. Posterior view

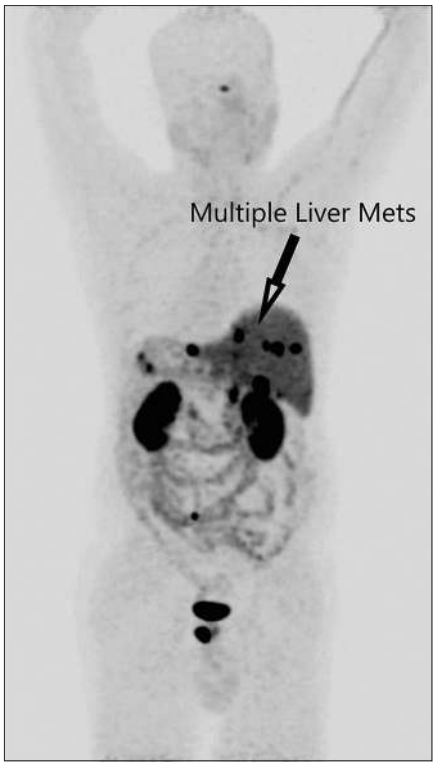


**Figure 4:** $^{68}$Ga-DOTATATE PET CT study of the same gentleman at the end of chemotherapy with uptake in multiple liver lesions and left pubic bone - progression. Posterior view

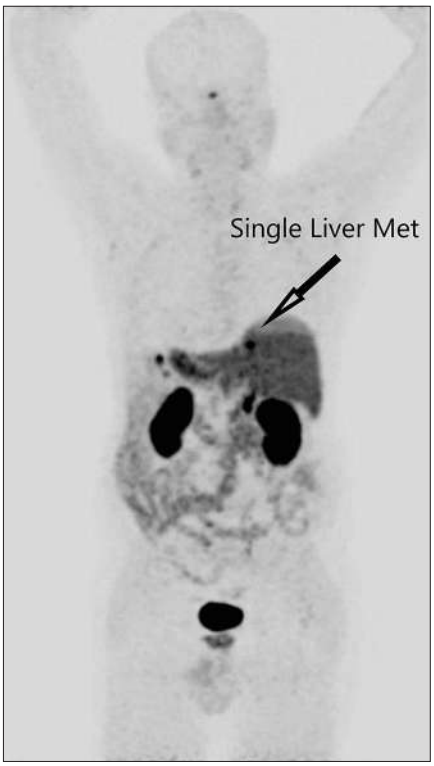


**Figure 5:** $^{68}$Ga-DOTATATE PET CT study of the same gentleman, post 4 doses of $^{177}$Lu DOTATATE therapy showing Regression of $^{68}$Ga-DOTATATE avid single liver lesion. Posterior view

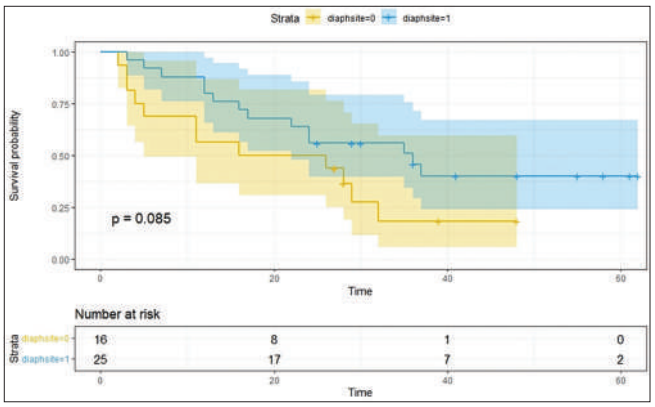


**Figure 6:** Overall survival after classifying the site of the tumor in relation to the diaphragm showed an advantage if the tumor was situated below the diaphragm. Overall survival: Blue-below diaphragm; Yellow-above diaphragm

due to the greater availability of screening, and access to healthcare facilities. Nevertheless, they are often diagnosed at an advanced stage, wherein surgery alone cannot be a definitive option for cure. Such patients might benefit from PRRT as an adjuvant therapy.

Our study evaluated the benefits of PRRT, taking into account the symptomatic, biochemical, and imaging response.

The demographic characteristics of this study, including male preponderance, were comparable to other similar studies.[9,10]

**Table 5: Treatment response: Table showing benefits after PRRT, based on clinical, biochemical response, and imaging evaluation**

| | No |
|---|---|
| Imaging | |
| Regression | 1 |
| Progression | 13 |
| Static image with metabolic response | 18 |
| Data not available | 9 |
| Delta Decrease in Chromogranin A from Baseline | |
| Upto 30% | 1 |
| More than 30% | 8 |
| Normalized | 2 |
| Increased | 11 |
| Data not available | 19 |
| Symptomatic response from clinical symptoms | |
| Asymptomatic | 35 |
| Worsened | 1 |
| Fever and Neutropenia* | 2 |
| Lost to follow up | 3 |
| Overall benefit (any two criteria) | |
| Yes | 29 |
| No | 8 |
| Lost to follow up | 4 |

*Patient presented with fever and was found to have mild neutropenia which resolved with supportive measures

Unlike other studies, the current study showed the pancreas and small bowel as the primary site for NET.[11] This could be due to a referral bias, as our hospital is a large tertiary care center. Available literature mentions the bowel and lungs as the primary sites of NET. However, recent studies have shown an increasing trend of primary pancreatic NET,[12] probably due to an increase in imaging studies. In our study, the most affected organ due to distant metastasis was the liver, which was noted in other studies too.[13]

Elevated serum Chromogranin A levels reflect the disease extent and tumor burden.[14] Patients in our study demonstrated a wide range of elevated Chromogranin A levels. Following PRRT, the response of serum Chromogranin A levels was shown to be of prognostic significance in predicting survival outcomes.[15] Studies have shown that Chromogranin A level has prognostic value in determining outcomes in primary NET of the gastrointestinal tract[16] and in resectable pancreatic mass, but not in advanced, inoperable cases.[17] However, our study did not reveal any overall survival benefit in those with lower serum levels of Chromogranin A.

The survival benefits of PRRT in NETs have been well documented, even in extensive disease after multiple prior treatments[18] with very minimal toxicity.[19] Our study revealed comparable responses in terms of evaluation, with imaging,[20] biochemical,[21] and symptomatic improvement.[22] Comparable similar results were demonstrated in other centers in our country.[23] The overall benefit of PRRT in patients even with extensive disease, who were already treated with multiple prior

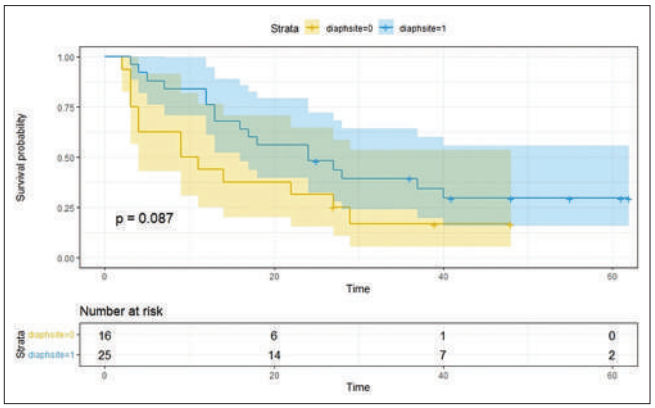


**Figure 7:** Progression-free survival after classifying the site of the tumor in relation to the diaphragm showed an advantage to those tumors situated below the diaphragm similar to that shown in overall survival. Progression-free survival: Blue, below diaphragm; Yellow, above diaphragm

treatments, was evident and similar to previously published studies.[24] There is a need to consider PRRT as a safe treatment modality, even before chemotherapy in select patients, as it may contribute to a better quality of life, given its minimal side effects.

Studies of NETs with lymph node metastases, which is also an independent prognostic marker,[25] have shown decreased survival,[26] with increased postoperative recurrence.[27] Large tumor size is also reported to be a predictor of lymph node involvement.[28] Hence, surgical resection of all possible nodes is recommended.[29] In our study, patients with nodal metastasis had higher Cg A levels than those without nodal involvement. However, there was no difference in the survival benefit between these groups, implying that PRRT is effective, irrespective of nodal involvement.

Patients without lung metastases had a better survival benefit than those with pulmonary involvement. However, studies have shown that patients with pulmonary involvement receiving PRRT have a definite survival advantage.[30]

None of our patients had any major adverse events following PRRT, and most of them had better tolerability in comparison to other treatments (surgery, radiation therapy, and chemotherapy) received. Considering the advanced nature of the disease at diagnosis, PRRT has value as a good adjuvant therapy amongst those having a residual tumor following their primary therapy or inoperable tumor.

The limitations of our study include the small number of patients, short duration follow-up, and the lack of a control arm. The retrospective nature of the study also limits the possibility of randomization of patients into study groups.

## Conclusion

This study aimed to evaluate the benefit of $^{177}$Lu-DOTATATE PRRT in patients with progressive metastatic NET and to study survival in terms of multi-organ involvement. Our study found that the main site of primary NET is in the pancreas, and the most common site for metastases is the liver. Considering

radiological and clinical responses, the overall benefit was noticed in most patients. Despite symptomatic improvement, there was no significant survival benefit for those with pancreatic, liver, or nodal metastasis. There was negligible toxicity, impelling us to consider PRRT as the first-line adjuvant therapy for those with metastatic NET. However, further randomized prospective studies, with a larger sample size, are required to establish the utility of this modality as the first line option in treatment guidelines.

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## Authors' contribution

Dr David Mathew, Dr Felix K. Jebasingh, Dr Ashish Singh and Dr Regi Oommen were involved in conceptualizing the study and statistical analysis. Dr David Mathew, and Dr Justin Benjamin, were involved in gathering information. Dr David Mathew, Dr Saumya S. Sunny, Dr Justin Benjamin, Dr Junita R. John, and Dr Regi Oommen were involved in investigations including nuclear medicine scans and in the decisions of PRRT administration and post treatment management of the patients. Dr Josh T. Georgy was involved in statistics and representation of data. All authors were involved in writing, revision, reading and approving the manuscript for publication.

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## Conflicts of interest

There are no conflicts of interest.

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