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Surgical feasibility, Determinants and overall Efficacy assessment of Neoadjuvant PRRT with ^{177}Lu-DOTATATE for Locally Advanced Unresectable Gastroenteropancreatic Neuroendocrine Tumors

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Running Title: Neoadjuvant PRRT with ^{177}Lu-DOTATATE – A single centre experience

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ABSTRACT

OBJECTIVE

The aim of the study was to assess ^{177}Lu-DOTATATE peptide receptor radionuclide therapy (PRRT) in neoadjuvant setting in gastroenteropancreatic neuroendocrine tumors (GEP-NETs). In addition, we also evaluated the variables associated with resectability of the primary following PRRT.

MATERIALS AND METHODS

A total of 57 GEP-NETs with unresectable primary due to vascular involvement as defined using the National Comprehensive Cancer Network (NCCN) criteria given for pancreatic ductal adenocarcinoma (PDAC), who underwent ^{177}Lu-DOTATATE without any prior surgery were included in this study. GEP-NETs were divided into two groups: Group1- without liver metastases (n=23 patients) and Group2- with potentially resectable liver metastases (n=34 patients). ^{177}Lu-DOTATATE was administered with mixed amino acid-based renal protection with dose of 7.4 GBq (200 mCi) per cycle. Evaluation of surgical resectability following PRRT was done by using tri-phasic computed tomography (CT) imaging. Overall PRRT response was evaluated under four broad categories. The Kaplan–Meier product-limit method was used to calculate progression free survival (PFS) and overall survival (OS). Associations between variables and resectable primary after PRRT were analyzed by using Chi-square test at significant P value less than 0.05.

RESULTS

Following ^{177}Lu-DOTATATE, unresectable primary became resectable in 15 out of 57 (26.3%) patients {7 patients in group-1 and 8 patients in group-2}. Response (complete response and partial response) to PRRT was seen in 48 patients (84%), 23 patients (40%), 18 patients (31%) and 23 patients (40%) on symptomatic, biochemical, molecular imaging and anatomical imaging response evaluation criteria respectively. Estimated rates of PFS were 95% and 90% at 2 years in group1 and group2 patients respectively. The 2-years OS of combined both groups was 92.1%. Higher rate of resectable primary following PRRT was found in duodenal NET, GEP-NETs with absent regional lymph node involvement, size of

primary<5cm, size of liver lesions ≤1.5 cm, number of liver lesions ≤3 and FDG uptake(SUVmax<5 in primary tumor) with significant P value.

CONCLUSION

Thus, unresectable primary converted could be into resectable in a moderate fraction of GEP-NETs following ^{177}Lu-DOTATATE, signifying that neoadjuvant PRRT could be considered in GEP-NETs patients with unresectable primary due to vascular involvement with or without liver metastases. Effective control of symptoms with favorable morphological and functional imaging response and durable PFS and OS following ^{177}Lu-DOTATATE PRRT were important observation in our study, which may lead to less morbidity and mortality in these patients.

INTRODUCTION

Neuroendocrine tumors (NETs) represent a diverse group of neoplasms arising from neuroendocrine cells located in many different sites throughout the body, most commonly in the gastro-pancreatic intestinal (Gastroenteropancreatic neuroendocrine tumors: GEP-NETs) and respiratory systems. Multiple therapeutic options are available [1,2], therefore, maximum therapeutic benefit to patient would be achieved with involvement of multidisciplinary team which include medical oncologists, surgeons, gastroenterologists, radiologists and nuclear medicine physician.

In NET, surgery is only definitive curative treatment option. The 5-years survival rate is more than 60 % in patients who present with resectable GEP-NETs, whereas it drops to less than 30% in unresectable tumors[3-9]. Aggressive surgical resection of primary and also metastatic liver lesions may improve symptoms and overall survival (OS) in GEP-NETs. However, resectability of primary in GEP-NETs is dependent on presence or absence of major abdominal vascular involvement, size and infiltration of tumor into other adjacent tissues[6, 8, 10, 11].

Targeted radionuclide therapy such as peptide receptor radionuclide therapy (PRRT) with radio-labeled somatostatin analogues, e.g. ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE has the advantage of selective treatment effect due to the use of an appropriate ligand carrying the radioisotope directly to the tumor cell population, in somatostatin receptor positive GEP-NETs[12]**.** PRRT has been reported to result into either disease stabilization, or partial remission, or even a reduction of tumor mass (upto more than 50%) in these patients[13]. Thus, PRRT has been employed as neoadjuvant therapy to decrease size of tumor in a few case reports and studies on NET[14-16].

The aim of our study was to assess the performance of ^{177}Lu-DOTATATE PRRT as neoadjuvant therapy in unresectable primary due to vascular involvement without liver metastases or with potentially resectable liver metastases in GEP-NETs. In addition, we also

evaluated overall efficacy of PRRT with the help of other response evaluation parameters and determined various variables associated with resectability of primary tumor following PRRT.

MATERIALS AND METHODS

Patients Population

Histopathologically proven cases of GEP-NETs with unresectable primary due to vascular involvement without liver metastases or with potentially resectable liver metastases, who had undergone ^{177}Lu-DOTA-octreotate PRRT without any prior surgical intervention for GEN-NETs were included and analyzed in this study.

An unresectable primary due to vascular involvement in GEP-NETs was defined using the National Comprehensive Cancer Network (NCCN) criteria given for pancreatic ductal adenocarcinoma (PDAC)[17] and these GEP-NETs were classified as locally advanced when there was tumor involvement of more than 180° of the circumference of one or more of the following blood vessels: superior mesenteric artery (SMA), celiac trunk, aorta, inferior vena cava (IVC), portal vein(PV), or superior mesenteric vein(SMV); presence of thrombosis of the porto-mesenteric venous system and un-reconstructable SMV-PV occlusion.

GEP-NET patients treated with PRRT, but presented with distant metastatic disease or extensive bi-lobar liver metastatic disease or who have undergone surgical intervention of primary tumor before PRRT and also those who were not treated with PRRT, were excluded from this study.

In this study, patients with GEP-NETs were divided into two groups based upon the presence or absence of metastatic liver disease: Group1-unresectable primary without liver metastases and Group2-unresectable primary with potentially resectable liver metastases. The patient characteristics were demonstrated in table 1. In group-1, grade-1 tumors were present in 10 patients and grade-2 tumors in 13 patients. In group-2, grade-1 tumors were

present in 16 patients, grade 2 tumors present in 17 patients and grade 3 tumor in 1 patient. In this study population, all GEP-NETs patients except one patient were well-differentiated NET. One patient had poorly-differentiated NET.

This study was approved by the Institutional Scientific Committee (ISC) and Institutional Ethics Committee (IEC). The waiver for informed consent was obtained in view of the retrospective nature of the study.

PRRT Regimen

GEP-NET patients had undergone tri-phasic abdominal CeCT and dual tracer PET-CT (^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT) before start of PRRT. ^{177}Lu-DOTATATE was administered in patients with unresectable primary (SSTR positive GEP-NETs on ^{68}Ga-DOTATATE PET-CT with krenning score ≥3, compared on MIP, coronal and transaxial images) due to vascular involvement without liver metastases or with potentially resectable liver metastases as per the Institutional neoadjuvant PRRT protocol with mixed amino acid-based renal protection with dose of 7.4 GBq (200 mCi) per cycle and the cycles were repeated at intervals of 8 to 10 weeks.

Surgical Resectability Evaluation

The surgical resectability evaluation following PRRT was done by using abdominal tri-phasic CT imaging after initial 2 cycles of PRRT at 4 months following first cycle of PRRT and after completion of PRRT cycles (4-5 cycles) at 3 months following the last cycle of PRRT. The surgical resectability criteria given by NCCN for PDAC were employed in this study, where decrease in size of tumor on tri-phasic CeCT imaging with clear fat planes around major abdominal vessels or tumor involvement less than 180° of the circumference vessel of the SMV/PV, celiac trunk or SMA or hepatic artery (HA) and also feature of short-segment encasement/occlusion of the SMV or PV amenable to vascular resection and reconstruction following PRRT was defined as resectable primary.

Overall Response Evaluation

After PRRT administration, all patients were followed up with ^{68}Ga-DOTATATE PET/CT for the post-treatment response evaluation in addition to being evaluated for symptomatic and biochemical responses {serum chromogranin-A (CgA) level}.

PRRT response was evaluated under four broad categories, (a) symptomatic response (b) biochemical response (serum CgA level), (c) objective response using molecular imaging (^{68}Ga-DOTATATE PET/CT), and (d) objective response using anatomic imaging (tri-phasic CT scan).

(a) Symptomatic response evaluation

For symptomatic response evaluation at follow-up, the patients were enquired with direct questioning on a scale of 0-100%, as to whether the tumor-related symptoms had 'disappeared'90-100% improvement (complete response-CR) or 'improved'30-89% improvement (Partial response-PR), or were 'stable'<30% improvement or <30% deterioration (stable disease-SD) or 'worsened'≥30% increase in symptoms or new symptoms (progressive disease-PD) compared to the baseline.

(b) Biochemical response evaluation

Biochemical response was assessed in all GEP-NETs by using serum CgA levels. Baseline values of this biochemical marker before start of PRRT were measured and the percentage change at the time of analysis was calculated. More than a 75% reduction or normalization of level in biochemical marker was considered as CR, 30-75% reduction as PR, <30% reduction to <30% increase as SD, and ≥30% increase in the levels as PD.

(c) Objective scan response evaluation: Molecular imaging

Molecular imaging response evaluation was undertaken in all GEP-NETs by using ^{68}Ga-DOTATATE PET/CT scans with help of the PET Response Criteria in Solid Tumors (PERCIST) criteria.

(d) Objective scan response evaluation: Anatomical imaging

Response Evaluation Criteria in Solid Tumors (RECIST 1.1) was used to evaluate anatomical imaging response.

Progression free survival and overall survival

The progression free survival (PFS) and overall survival (OS) were also assessed and calculated in the studied patient population. The PFS was defined as the time from first cycle of PRRT to documented disease progression on imaging study and OS was defined as time from first cycle of PRRT to death of patient. If death did not occur during the observation period, survival time was censored at the last date the respective subject was known to be alive.

Statistics

The patient characteristics were tabulated and summarized by both count and percentage. The number of patients with resectable primary following PRRT was calculated. The overall efficacy of PRRT under four broad categories was calculated by determining CR, PR, SD and PD in each categories. The median point estimate with 95% confidence interval (CI) for PFS and OS were calculated by the Kaplan–Meier method. The PFS curves for group-1 and group-2 patients were determined by using the Kaplan–Meier product-limit method.

The Chi-square test was used to test the association between categorical types of variables and resectable primary (after PRRT). P value less than 0.05 considered to be statistically significant for this analysis. The following variables were investigated for association with resectable primary after PRRT: age of patients at start of PRRT (20-45yr, 46-60yrs, ≥61yrs),

site of primary (1= Pancreas, 2=Duodenal, 3=Jejunal, 4=Ileal), total cumulative radionuclide dose (1=400-600mCi, 2=601-800mCi, 3=801-1100mCi), number of PRRT cycles (1=2cycles, 2=3-4cycles, 3=5cycles), MIB-1 index (1=<3%, 2=3-20%, 3=>20%), previous chemotherapy and previous octreotide analogue therapy (received versus not received), regional lymph nodal involvement (involved versus not involved), baseline size of the primary tumor (1=<5cm, 2=5-7 cm, 3=>7cm), baseline ^{68}Ga-DOTATATE uptake (1=SUVmax<20, 2=SUVmax20-50, 3=SUVmax>50) and FDG uptake (1=SUVmax<5, 2=SUVmax5-7, 3=SUVmax>7) in primary. Additionally following variables were evaluated in group-2 patients, i.e. baseline ^{68}Ga-DOTATATE uptake and FDG uptake, size (1=≤1.5cm, 2=1.6-3.5cm, 3=>3.5cm) and number of liver lesions (1=≤3, 2=4-6, 3=≥7).

RESULTS

A total of 57 GEP-NETs were included and analyzed in this study. These 57 patients divided into two groups: Group-1 included 23 patients and Group-2 included 34 patients as depicted in table 1.

In the present study, pancreatic NET {32patients (56%)} was the most common site of primary. The head and body of pancreatic regions were the most common location involved by tumor seen in 27patients (47%).The SMV/ PV were commonly involved blood vessels by the tumor seen in 35patients (61%) and involvement of SMA by the tumor seen in 27patients (47%). Before PRRT, size of primary GEP-NETs ranged from 3.5 to 11 cm with average of 5.8cm in group-1 and from 4 to 12 cm with average of 6 cm in group-2. Baseline size of liver lesions ranged from 0.8 to 5.6 cm with average of 3 cm was seen in group-2 patients. The MIB-1 labeling index ranged from 1 to 15 with median of 3 in group-1 and ranged 1 to 25 with median of 4 in group-2. All 57 patients were symptomatic before the start of PRRT with abdominal pain, vomiting, weakness and weight loss being the common complaints. Systemic chemotherapy and somatostatin analogue therapies were administered in 9 and 5 patients and 6 and 7 patients in groups 1 and 2 respectively and these patients showed unresponsive/progressive disease following chemotherapy and somatostatin analogue therapies before administering PRRT.

Total cumulative dose of ^{177}Lu-DOTATATE ranged from 14.8 to 40.7 GBq (400 to 1100 mCi) with average of 22.2GBq (600 mCi) per patient and 14.8 to 40.7 GBq (400 to 1100mCi) with average of 27.45GBq (742 mCi) per patient in group-1 and group-2 respectively. The administered PRRT cycles ranged from 2 to 5 cycles and average of 4 PRRT cycles per patient in this study.

Following PRRT, size of primary GEP-NETs ranged from 2.0 to 10 cm with average of 4.8cm in group1 and from 2.0 to 9.5 cm with average of 4.6 cm in group-2. Size of liver lesions ranged from 0.5 to 7 cm with average of 2.4 cm was seen in group-2 patients after PRRT therapy.

PRRT was well tolerated in all 57 GEP-NETs without any major hematologic and renal toxicity in any of these patients, except for two patients in group-1 and one patient in group-2, who showed mild grade I hematological toxicity and renal toxicity respectively during the initial PRRT cycles and which recovered in subsequent follow-up.

Surgically Resectable Primary Following PRRT

The resectability criteria given by NCCN for PDAC were employed in this study following PRRT in GEP-NETs patients. After use of PRRT in GEP-NETs, unresectable primary became resectable in 7 (2 patients= pancreatic NET, 3 patients =duodenal NET, 2 patients =ileal NET) out of 23 patients in group-1 and 8 (4 patients= pancreatic NET, 3 patients=duodenal NET, 1 patient=jejunal NET) out of 34 patients in group-2as per the NCCN resectability criteria. Thus, the overall resectable primary tumor following PRRT (combining both groups) was seen in15 patients (26.3%) out of 57. Repeat imaging for resectability assessment was done after 2 cycles in all 57 patients and then after 4-5 cycles in 56 patients; out of the 15 patients who became operable after PRRT, 1 patient became operable after 2 cycles of PRRT, while 14 patients became operable after 4-5 cycles.

Overall PRRT Response under Four Broad Categories

(a) Symptomatic response:

All GEP-NET patients had symptomatic disease before initiating PRRT. After PRRT, 19 out of 23 patients had CR (82.8%), 1 out of 23 patients had PR (4.3%), 2 out of 23 patients had SD (8.6%) and 1 out of 23 patients had PD (4.3%) in group1.
In group-2, 24 out of 34 patients had CR (70.5%), 4 out of 34 patients had PR (11.9%), 3 out of 34 patients had SD (8.8%) and 3 out of 34 patients had PD (8.8%) on symptomatic response evaluation.

(b) Biochemical response:
After PRRT therapy, no CR observed in any of the GEP-NET patients, 10 out of 23 patients had PR (43.5%), 10 out of 23 patients had SD (43.5%) and 3 out of 23 patients had PD (13%) in group-1.
In group-2, no CR found in any, 13 out of 34 patients had PR (38.2%), 18 out of 34 patients had SD (53%) and 3 out of 34 patients had PD (8.8%) on biochemical response evaluation.

(c) Objective response using molecular imaging:

After PRRT therapy, 1 out of 23 patients had CR (4.3%), 8 out of 23 patients had PR (34.8%), 12 out of 23 patients had SD (52.3 %) and 2 out of 23 patients had PD (8.6%) in group1 using PERCIST criteria.
In group-2, no CR found in any patient, 9 out of 34 patients had PR (26.5%), 24 out of 34 patients had SD (70.5%) and 1 out of 34 patients had PD (3%) on PERCIST criteria.

(d) Objective response using anatomical imaging:

After PRRT therapy, no CR was found in any of the GEP-NET patients, 7 out of 23 patients had PR (30.4%), 15 out of 23 patients had SD (65.3 %) and 1 out of 23 patients had PD (4.3%) in group-1 using RECIST 1.1 criteria.
In group-2, no CR was found in any patient, 16 out of 34 patients (example shown in fig 1) had PR (47%), 15 out of 34 patients had SD (44.1%) and 3 out of 34 patients had PD (8.9%) on RECIST 1.1 criteria as shown in table 2.

Progression free survival (PFS) and overall survival (OS)

The median PFS and OS were not reached in this study with median follow-up period of 24 months. Estimated rates of PFS were 95% and 90% at 2 years in group-1 and group-2 patients respectively (as shown in fig-2 and fig-3). No morality was found in group-1, whereas one patient died in group-2.The 2-years OS of combined both groups was 92.1%.

Association of Tumor Resectability Following PRRT

Association between resectable primary following PRRT and various variables were evaluated in this study and we found significant P value for following variables:(i) site of primary (duodenal NET) (ii) regional lymph nodal involvement (no involvement), (iii) size of primary (<5 cm), and (iv) baseline FDG uptake in primary(SUVmax< 5) for combined both group-1 and group-2. For group-2, (i) size of the liver lesions (≤1.5 cm) and (ii) number of liver lesions (≤3) had significant P value.

DISCUSSION

In GEP-NETs, surgery offers only chance for cure and aggressive surgical resection of tumor has been reported to be resulted into long-term survival with acceptable associated morbidity and mortality risks. Neoadjuvant therapy is intended to achieve reduction of the tumor size, enabling surgical resection of many gastrointestinal cancers and is mostly based upon chemotherapy, radiation therapy and or hormonal therapy. Treatment options are limited in patients with unresectable and locally advanced GEP-NETs. For these tumors, chemotherapy has limited efficacy with high incidence of significant side effects[18]. Biological therapy with somatostatin analogues and interferon-alpha can reduce symptoms but fails to produce an objective response of tumor shrinkage in these tumors in neoadjuvant setting[19].

Somatostatin analogues labeled with radionuclides has been used in diagnosis and therapy of GEP-NETs as these tumors express somatostatin receptor on their surface. PRRT has been employed in disseminated metastatic and unresectable GEP-NETs with positive

somatostatin receptor expression confirmed by molecular imaging. ^{177}Lu-DOTATATE PRRT has been shown promising response and survival rates with minimal associated toxicity[13], [20, 21]. A few reports available in literature that demonstrated use of pre-operative PRRT in unresectable pancreatic NET for reducing size of tumor and enabling surgical intervention in these tumors[14-16].

One particularly challenging aspect in GEP-NETs is defining resectable and unresectable primary tumor, which often is subjective and surgeon-dependent. Hence, in our study, we use objective resectability criteria (given by NCCN for PDAC) for determining resectability of primary tumor (as shown in fig2 and fig 4).GEP-NETs patients described in our study were all deemed unresectable primary before PRRT by a surgeon with expertise in GI and Hepato-Pancreato-Biliary (HPB) surgery[22]. PRRT is generally well tolerated as compared to chemotherapy and other treatment modalities in GEP-NETs. Similarly in our study, ^{177}Lu-DOTATATE PRRT was well tolerated without major hematological and renal toxicities in any of the patients. In our study, by using objective resectability criteria in GEP-NETs, unresectable primary tumor became resectable following ^{177}Lu-DOTATATE PRRT in 7 patients (30.43%) in group1 and 8 patients (23.5%) in group-2. Results of our study were similar to results of other series reported in literature for NET cases[23].

Barber et al[15] used ^{177}Lu-octreotate as neoadjuvant PRRT in five patients, four patients with pancreatic NET confined to local or loco-regional sites and one patient with duodenal NET with solitary liver metastasis. In their study, PRRT were administered with a concurrent radio-sensitizing dose of Fluorouracil (5FU) chemotherapy (200 mg/m^2/24 h) commencing 4 days prior and continuing for a total of 3 weeks in four patients and with prior to external-beam radiotherapy (45 Gy in 25 fractions) in remaining one patient to maximize radiation dose delivery to the tumor. In their study, all five patients showed good response to PRRT and one patient underwent curative surgery following neoadjuvant PRRT.

van Vlietet al[16] in their study, demonstrated use of ^{177}Lu-octreotate PRRT as neoadjuvant therapy in 29 pancreatic NET patients with a borderline or unresectable primary with or

without oligo-metastatic liver lesions. They found extensive vascular involvement of primary tumor, portal and mesenteric vein thrombosis before start of PRRT. They suggested that sufficient venous collateral formation may develop during course of PRRT cycles and this leads to surgical resection of primary tumor with safe and easy reconstruction of the portal and mesenteric veins because of intact collateral circulation. In their study, surgery was performed in 9(31%) out of 29 patients following neoadjuvant PRRT.

Stoeltzing et al[24] and Sowa-Staszczaket et al[14] studied use of neoadjuvant PRRT with help of ^{90}Y-DOTATOC and ^{90}Y-DOTATATE in pancreatic NET with metastatic liver lesions respectively. Significant regression of liver lesions following neoadjuvant PRRT was seen in their study and this facilitated surgical removal of liver lesions. Similarly, in our study average size of liver lesions changed from 3 cm to 2.4 cm following ^{177}Lu-DOTATATE PRRT with PR anatomical imaging response in 16 (47%) out of 34 patients. This will be helpful for surgical intervention in these patients with liver metastases as shown by Stoeltzing et al[24] and Sowa-Staszczaket et al[14] in their studies.

Partelliet et al[25] adopted neoadjuvant PRRT in 23 pancreatic NET patients with features of high disease recurrence. They found that size of the primary pancreatic tumor decreased following neoadjuvant PRRT and also low risk of pancreatic fistula development (after surgery) and low incidence nodal metastases (at time of surgery)in neoadjuvant PRRT treated group as compared to group treated with upfront surgery. Similarly, in our study average size of primary tumor changed from 5.8 cm to 4.8 cm and from 6.0 cm to 4.6 cm in group-1 and group-2 respectively. This could also facilitate surgery with low incidence of nodal metastases and low risk of pancreatic fistula formation at the time of surgery or thereafter respectively as mentioned by Partelliet et al[25], reducing the risk of morbidity and mortality associated with surgery.

We evaluated association between resectable primary following PRRT and various variables in this study. The significant P value was found for following variable variables; site of primary (duodenal NET), regional lymph node involvement (absent), baseline size of

primary tumor (<5cm), baseline size (≤1.5cm) and number (≤3) of metastatic liver lesions, and baseline FDG uptake (SUVmax<5) in primary tumor. GEP-NET patients having these variables have high rate of resectable primary following PRRT in our cohort study.

In our study, CR on symptomatic response evaluation was reported in 19 patients (82%) and 24 patients (70%) in group-1 and group-2 respectively, which indirectly shows improvement in global health status and quality of life in these patients after PRRT. We observed PFS of 95% and 90% in group-1 and group-2 respectively and OS of 92.1% in both groups at 24 months following PRRT. The observed longer PFS and OS following PRRT may have additional importance in patient care management in this group of GEP-NETs.

The limitation of our study was its retrospective nature, non-fixed total cumulative dose of ^{177}Lu-DOTATATE and variable number of PRRT cycles. However, the average were of usual range for PRRT viz. an average of 4 PRRT cycles per patient and total cumulative dose 22.2GBq (600 mCi) and 27.45GBq (742 mCi) per patient in group-1 and group-2 respectively. These average total cumulative doses of ^{177}Lu-DOTATATE and average number of PRRT cycles administered in our study were similar to doses and number of PRRT cycles reported in other neoadjuvant PRRT studies.

CONCLUSION

Neoadjuvant ^{177}Lu-DOTATATE PRRT can be a useful treatment modality in GEP-NETs patients with unresectable primary due to vascular involvement without liver metastases or with potentially resectable liver metastases, as unresectable primary became resectable in a moderate fraction of GEP-NETs patients following ^{177}Lu-DOTATATE PRRT. ^{177}Lu-DOTATATE PRRT can be considered as safe treatment modality without high incidence of major hematological or renal toxicity and this would likely be helpful in reducing overall morbidity and mortality associated with surgery and/or other treatment modalities. The result of our study showed favorable morphological and functional imaging response in majority of patients and these patients became symptom-free after ^{177}Lu-DOTATATE PRRT. The success rate of tumor resectability following PRRT was dependent upon site of primary, regional

lymph node involvement, size of primary tumor, size and number of liver metastatic lesions(in GEP-NET patients with liver metastases), and FDG uptake in primary tumor.

KEY POINTS

QUESTION: Exploring in real-life clinical scenario the performance and role of neoadjuvant PRRT with ^{177}Lu-DOTATATE in patients with locally advanced, unresectable GEP-NETs with unresectable primary due to vascular involvement without liver metastases or with potentially resectable liver metastases.

PERTINENT FINDINGS: In this observational study estimated at large volume tertiary cancer care centre, unresectable primary became resectable in a moderate fraction of GEP-NET patients (26%) following ^{177}Lu-DOTATATE PRRT. The success rate of tumor resectability following PRRT was dependent upon site of primary, regional lymph node involvement, size of primary tumor, size and number of liver metastatic lesions (in GEP-NET patients with liver metastases), and FDG uptake in primary tumor.

IMPLICATIONS FOR PATIENT CARE: The work addresses the role of PRRT with neoadjuvant intent, an area of significant clinical interest in the parlance of GEP-NET esp. from the GI surgeon's perspective of selecting patients for PRRT as a potentially useful treatment option in Neoadjuvant setting.

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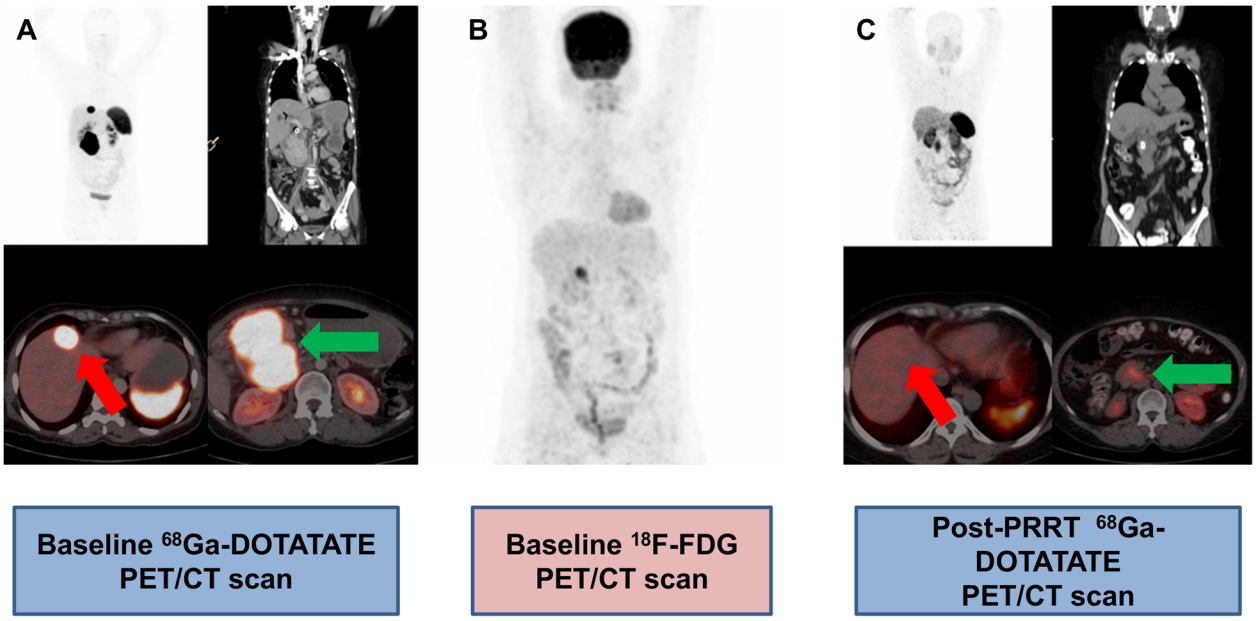

Fig 1. A 56 years old women, known case of unresectable pancreatic NET with single liver metastatic lesion. Baseline ^{68}Ga-DOTATATE PET/CT scan (A) showed intensely somatostatin receptor avid unresectable primary pancreatic lesion (measuring 8.0x8.8 cm) involving PV/ SMV (> 180°) and intensely somatostatin receptor avid single metastatic lesion measuring 2.5x2.8cm in segment IV of the liver. Baseline ^{18}F-FDG PET/CT scan (B)showed absent FDG uptake in primary and metastatic liver lesion. Patient received 5 cycles of PRRT (total cumulative dose=33.3GBq). Post -PRRT, ^{68}Ga-DOTATATE PET/CT scan (C) showed complete morphological disappearance of metastatic liver lesion and significant reduction in size and ^{68}Ga-DOTATATE uptake of pancreatic lesion with no major abdominal vessels involvement and primary became resectable. Post-PRRT, patient underwent whipples procedure without any major complication in peri-operative period and on subsequent follow up period.

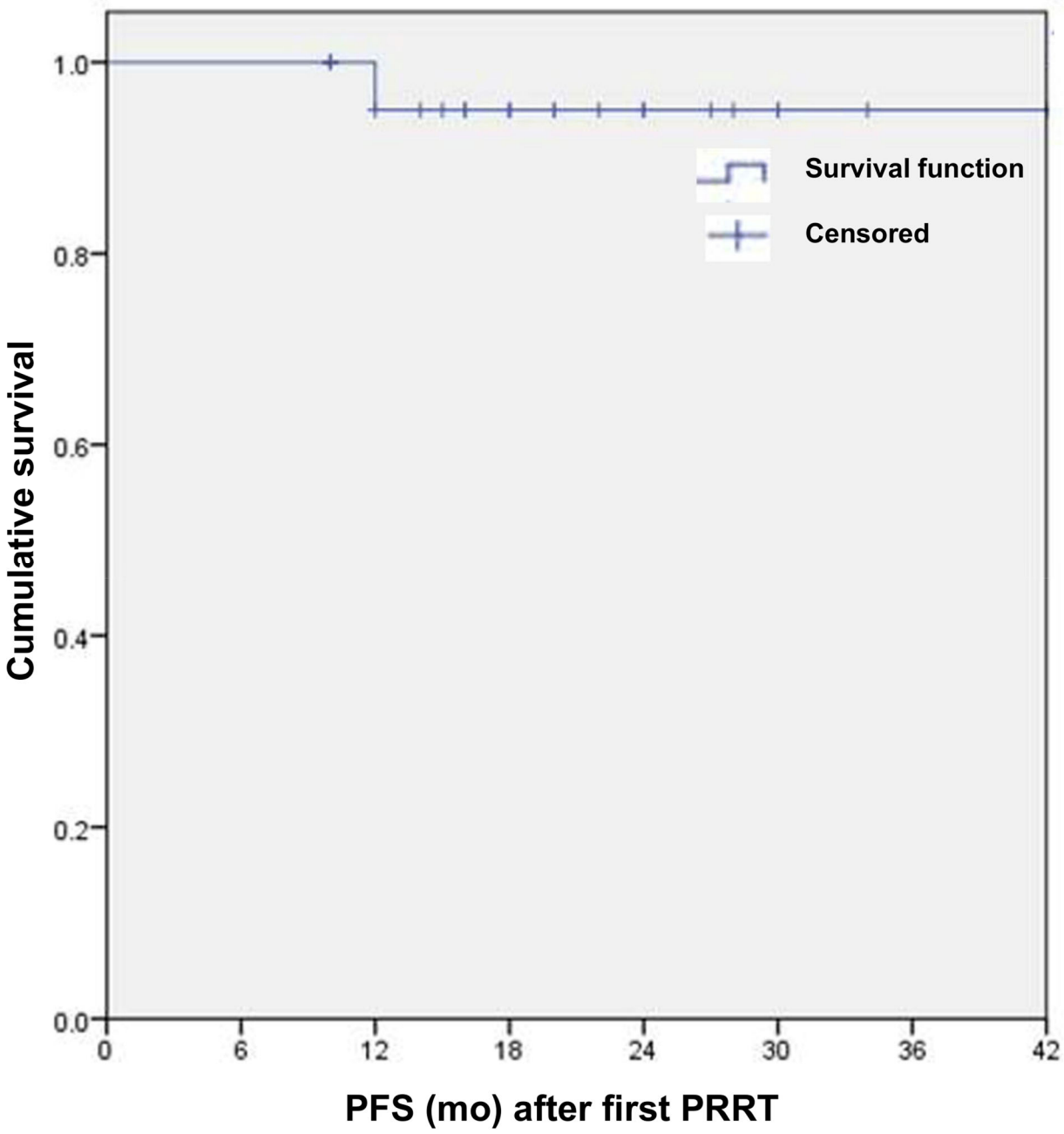

Fig 2. Kaplan-Meier curve of PFS in group1 patients

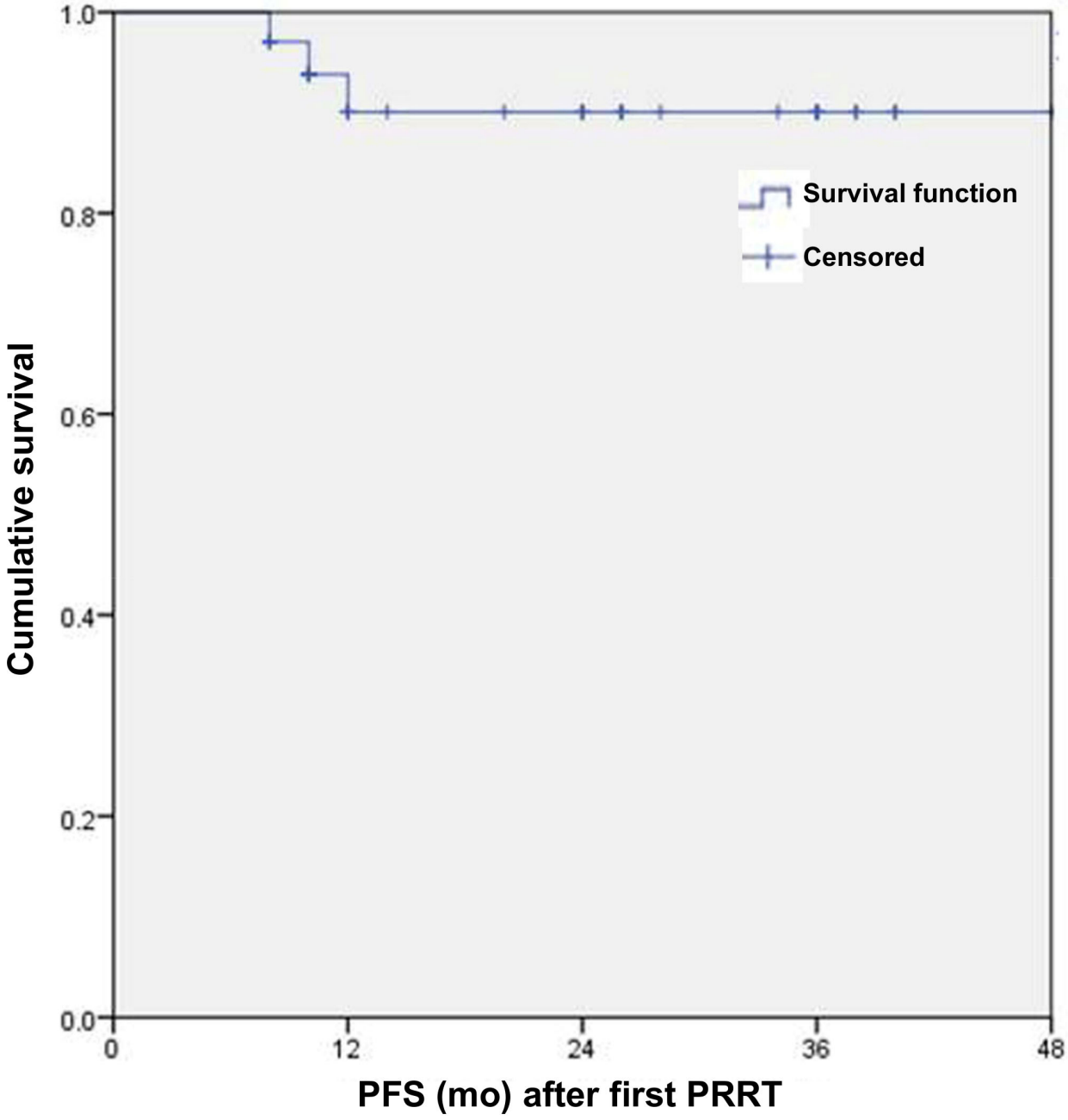

Fig 3. Kaplan-Meier curve of PFS in group2 patients

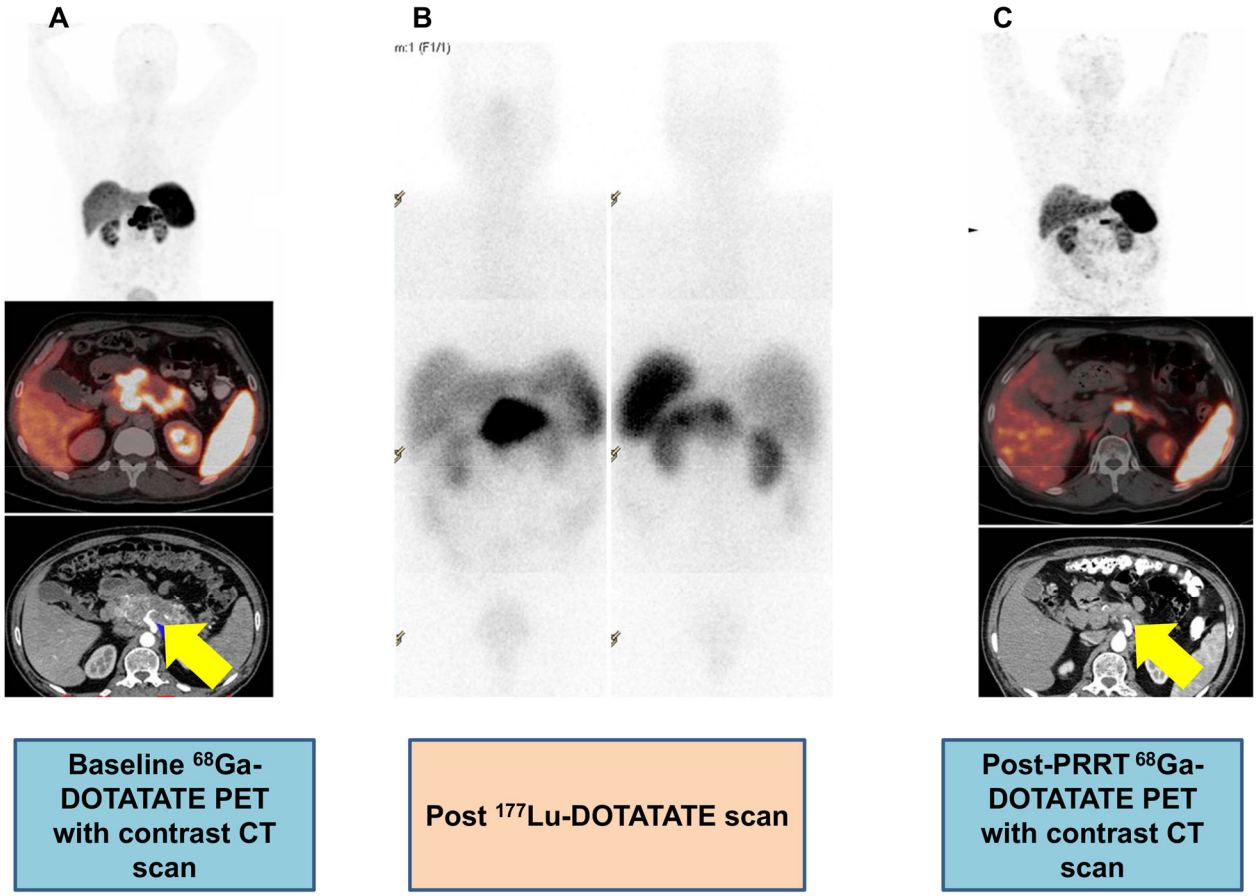

Fig 4. Unresectable pancreatic NET, baseline ^{68}Ga-DOTATATE PET with contrast CT scan (A) showed complete encasement (>180°) of celiac trunk by intensely somatostatin receptor avid pancreatic lesion (SUVmax80) measuring 7.0x6.6cm. Patient received PRRT (total cumulative dose of 31.45GBq). Post ^{177}Lu-DOTATATE scan (B) showed good tracer concentration in primary pancreatic lesion. Post-PRRT ^{68}Ga-DOTATATE PET with contrast CT scan (C) showed significant reduction in size (measuring 2.0x1.5cm) and ^{68}Ga-DOTATATE uptake (SUVmax30) of primary pancreatic lesion with less than 180° encasement of celiac trunk. Unresectable primary became resectable following PRRT in this case.

Table 1. Patient characteristics

Patient characteristics	**Group1**	**Group2**
Number of Patients	23	34
Sex (Male/Female)	15/8	18/16
Age, range in years (average)	30-76(52)	30-78(51)
Symptomatic patients before PRRT		
No. of patients	23	34
Prior therapies (No. of patients)		
1. Chemotherapy	9	6
2. Octreotide analogue	5	7
Primary sites (No. of patients)		
1. Pancreatic NET	12	20
2. Duodenal NET	4	8
3. Jejunal NET	1	4
4. Ileal NET	6	2
MIB-1 Index, range	1 to 15% (median 3%)	1 to 25% (median 4%)
Size of primary tumor before start of PRRT, range in cm (average)	3.5 to 11 cm (average 5.8cm)	4 to 12 cm (average 6 cm)
Size of metastatic liver lesions before start of PRRT, range in cm (average)	-	0.8 to 5.6 cm (average 3cm)
Total cumulative ^{177}Lu-DOTATATE dose, range with average	14.8 to 40.7 GBq(400 to 1100 mCi) with average of 22.2GBq (600mCi)	14.8 to 40.7 GBq(400 to 1100) with average of 27.45GBq(742 mCi)
Number of PRRT cycles range with average	2 to 5 cycles with average of 4 cycles	2 to 5 cycles with average of 4 cycles

Table 2.PRRT response under four broad categories in group-1 and group-2 patients

Response	Symptomatic evaluation		Biochemical evaluation		PERCIST*		RECIST 1.1**	
	Group 1(n=23)	Group 2 (n=34)	Group 1(n=23)	Group 2(n=34)	Group 1 (n=23)	Group 2(n=34)	Group 1 (n=23)	Group 2(n=34)
Complete response	19	24	0	0	1	0	0	0
Partial Response	1	4	10	13	8	9	7	16
Stable disease	2	3	10	18	12	24	15	15
Progressive disease	1	3	3	3	2	1	1	3

*PERCIST (PET Response Criteria in Solid Tumors) and **RECIST 1.1 (Response Evaluation Criteria in Solid Tumors)

Graphical Abstract