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Evaluation of survival outcomes in patients with sporadic, advanced, unresectable well-differentiated pancreatic neuroendocrine tumors treated initially with octreotide LAR and subsequent therapeutical approaches on relapse. A real-world data set

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ABSTRACT

Introduction. Somatostatin analogs (SSA) are widely used in the treatment of patients with well-differentiated neuroendocrine tumors (NET). There are limited reports about the role of octreotide LAR in first-line therapy of advanced pancreatic NET (pan-NET). This study aimed to evaluate the antiproliferative effect of octreotide LAR in patients with sporadic, advanced, unresectable pan-NET, based on progression-free survival (PFS).

Material and methods. This was a retrospective analysis of 374 patients with pan-NET; 41 treated subjects were included. The primary endpoint was PFS defined as the time to disease progression (Response Evaluation Criteria in Solid Tumors: RECIST). Univariate and multivariate analyses were used to identify predictors of PFS. Secondary endpoints included overall survival (OS) and second-line therapies after progression.

Results. There were 13 (32%) patients with G1 pan-NET and 28 (68%) with pan-NET G2, 21 female and 20 male, with mean age 55.4 (range 29–87). Median PFS was 9.0 months (95% CI 4.7–24.0). Subgroup analysis revealed that G1 and no-bulky liver disease (< 25% liver volume) were associated with significantly longer PFS. Univariate analysis confirmed a correlation between G1 [0.34 hazard rate (HR) of progression or death (95% CI 0.16–0.72)] and no-bulky liver disease HR = 0.31 (95% CI 0.13–0.71). Multivariable analysis demonstrated that only functional (secretory) pan-NET was associated as an independent factor with shorter PFS HR = 2.97 (95% CI 1.0–8.74). Median OS was 105.4 months (95% CI 40.0–172.0). After relapse following initial systemic therapy, the second line was used in 34 subjects, 3rd line in 18th, and 4th line in 9 subjects.

Conclusions. Octreotide LAR shows moderate antiproliferative activity in pan-NET. Prolonged PFS may be associated with G1 and low-volume metastatic liver disease. In patients with progressive disease, various treatment options were used, which resulted in median OS of 105.4 months.

Key words: neuroendocrine tumors, octreotide lar, overall survival, progression-free survival, real world data

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Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies whose incidence in the USA and Europe appears to be increasing (an estimated incidence: 5.25 cases per 100,000) [1]. Gastroenteropancreatic (GEP) NETs constitute approximately 55% of diagnosed cases, and approximately 12% of them are located in the pancreas [2]. At original diagnosis, most patients (60–80%) present with distal metastases, thus treatment options are limited [3].

Somatostatin analogs (SSA) are commonly used to treat symptoms associated with hormone hypersecretion and have a favorable safety profile [4, 5]. Octreotide LAR and the second synthetic analog Somatulin AG have demonstrated antiproliferative activity in NETs in several reports including a randomized placebo-controlled trial [5–10]. The PROMID trial was a placebo-controlled, double-blind, randomized study assessing the effect of octreotide LAR on the control of tumor growth in patients with metastatic, well-differentiated mostly G1 midgut NETs with the absence of pancreatic NET. Patients who received octreotide LAR had significantly prolonged median time to tumor progression (TTP): 14.3 months *vs.* 6 months in the control group [5]. Similar benefits were observed in a post hoc analysis of the RADIANT-2 study, where median progression-free survival (PFS) was 22.2 months in patients not treated previously with SSA and 13.6 months in patients who received SSA [11]. However, reports on the efficacy of octreotide LAR in NET of pancreatic origin and potential predictive factors of treatment response are very limited [7, 8].

The aim

The primary aim of our study was to evaluate the antiproliferative effect of octreotide LAR 30mg in patients with pancreatic NET (pan-NET) G1 and G2, based on median progression-free survival (PFS), and to search for factors affecting median PFS in this group of patients using a real-world data set. The secondary endpoints were to assess further therapeutical approaches after relapse following first-line Octreotide LAR therapy, with further analysis of median overall survival (OS) in long-term follow-up.

Material and methods

Trial design and interventions

This trial was a retrospective study on real-world data conducted in three Polish referral centers. We reviewed the patients' records April 2008 up to March 2022. This study was approved by an independent ethics committee at the University of Warmia and Mazury (No 59/2019) and registered on ClinicalTrials.gov (No NCT04331912). Informed consent was waived because of the retrospective nature of the study.

All patients were treatment na ve before the start of octreotide LAR 30mg i.m. injection which wa given every 28 days as an initial approach (monotherapy) after pathology confirmation and staging evaluation. The evaluation included the standard approach with performance status (PS) based on the ECOG/WHO scale and secretory profile of the disease. Subjects with at least 3 injections of octreotide LAR were included in this study. Indications for octreotide LAR therapy were advanced, sporadic, pancreatic pan-NET G1 and G2 (clinical stage III and IV only), unresectable primary tumor and/or local/distal spread of unresectable disease, or patients' refusal to have any type of surgery. Before treatment, overexpression of SST receptors was confirmed in all patients, using the whole body WB-multi SPECT/CT method ^{99m}Tc-(HYNIC, Tyr3)octreotide (TOC) (Tektrotyd®, National Centre for Nuclear Research-Polatom, Poland) or PET/CT utilizing 68Ga DOTATATE or DOTATOC (Netspot® or Somakit®; AAA/Novartis, CH).

Subjects

We retrospectively screened records of 60 patients with histologically confirmed welland moderately-differentiated pan-NET G1 (according to WHO 2017, Ki-67 < 3%) and G2 (Ki-67 ≥ 3% and < 20%). All histopathology results were reviewed by a pathologist interested in NET (KR-P) [12]. Sixteen patients were excluded from analysis due to hereditary syndromes (multiple endocrine neoplasia type 1 — MEN1, n = 14; *Von Hippel-Lindau syndrome VHL*, n = 2). In addition, 3 subjects with rapid disease progression with fewer than 3 doses of octreotide LAR were excluded (Fig. 1).

Data collection

The information collected from patient medical records included demographics, date of diagnosis, location of metastases, volume of liver metastases, Ki67 proliferative index, performance status (PS ECOG scale), baseline chromogranin A levels (CgA), surgical treatment before octreotide LAR treatment, and follow-up data. All patients had CT examinations of the chest, abdomen, and pelvis. In each case, computed tomography (CT) was performed after i.v. contrast enhancement, from 70 to 120 mL (1.2–1.4 mg/kg) of low-ionic contrast medium intravenously, at a rate of 3.5–4.2 mL/s. In cases when CT

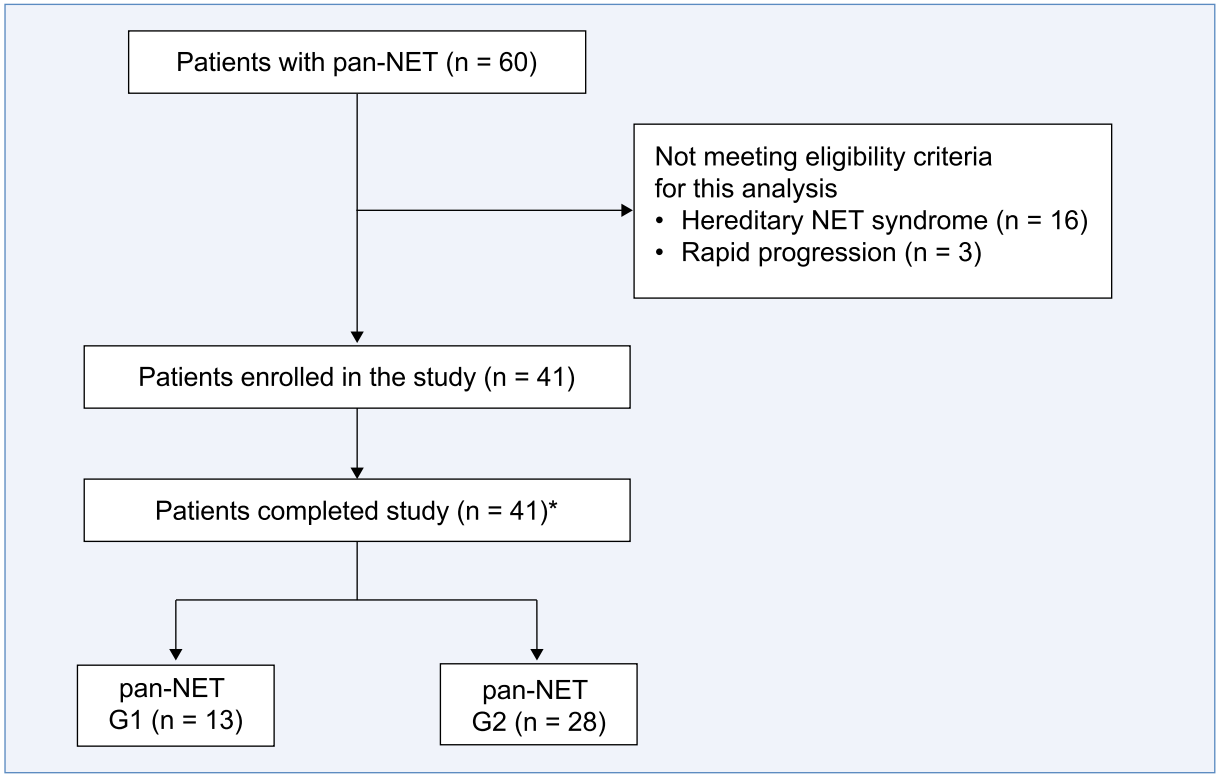


Figure 1. Study flowchart; *Patients who received at least 3 doses of octreotide LAR; pan-NET — pancreatic neuroendocrine tumor

was not possible, alternatively magnetic resonance imaging (MRI) before or after i.v. contrast enhancement was performed using the 1.5T and recent 3T systems. The response rate was evaluated using the same modality as initial CT or MRI at 6 month intervals and classified according to RECIST v.1.1 criteria. The objective response rate (ORR) was evaluated by two radiologists' (JMP & JBC) consensus. The initial tumor volume within selected 4–6 scan slices with the greatest tumor volume of all liver lesion(s) were selected and scored visually for the extent of disease and as tumor/liver ratio [13]. CgA concentrations were measured on the Kryptor system, BRAHMS GmbH kits, Thermo Fisher.

Assessments and endpoints

The primary objective of the study was to investigate the efficacy of octreotide LAR 30 mg administrated every 28 days based on estimation of median PFS evaluated using RECIST, defined as partial response (PR), stable disease (SD), or progressive disease (PD). Secondary endpoints included OS, the best objective response rate (BORR) during therapy and finding some predictive factors of PFS which might influence response to SSA. The details including endpoints and definitions with measurements are presented in Table 1.

Statistical analysis

Descriptive statistics on the study population (all randomly assigned patients who received at least three injections of octreotide LAR) were compiled for the data sets. The distributions of continuous variables were compared with the theoretical normal distribution using the Shapiro-Wilk test. The descriptive statistics were conducted: mean, standard deviation (SD), median, interquartile range (IQR), median PFS, and 95% confidence interval (CI). The differences between the subgroups were analyzed with either Student's t-test (for 2 subgroups with normal distribution) or the nonparametric Mann-Whitney test. To compare proportion in subgroups the chi-square test was used. Survival probabilities were estimated by the Kaplan-Meier method, and differences in survival were compared with the log-rank test. OS was defined as the time from histopathological diagnosis till death from any cause or last follow-up censored. PFS was calculated from the date of beginning treatment until the first evidence of progression, death, or last day of follow-up. Uniand multivariable predictors of PFS were estimated by Cox regression analysis. Univariate variables with p-value ≤ 0.1 were included in the multivariable model. A p-value < 0.05 was considered to be significant. The analysis was conducted using STATISTICA software (version 13.3) (TIBCO; CA: USA).

Table 1. Details including endpoints and definitions with measurements

Endpoint	Definition/measurement	Statistical analysis
Primary efficacy		
Median PFS	Time from first octreotide LAR 30 mg injection to progression or death from any cause	Kaplan-Meier method
Secondary efficacy		
Median OS	Time from initial diagnosis in subjects who had initial therapy using octreotide LAR 30 mg injection to death from any cause	Kaplan-Meier method
Best overall response	Best response recorded from finishing therapy to recorded disease progression RECIST 1.1 (DP)	Descriptive
Predictive factors of PFS	• Age (≤ 55 years[b] *vs.* > 55 years) • Sex (Male *vs.* Female) • BMI (< 25.0 *vs.* ≥ 25.0) • Initial (PS ECOG) before therapy • Tumor grade (G1 *vs.* G2) • Primary tumor size < 45 mm *vs.* ≥ 45 mm • Liver bulky disease with organ involvement (≤ 25% *vs.* > 25%) • Presence of bone mts (no *vs.* yes) • Secretory tumors *vs.* non-secretory tumors (yes *vs.* no) • Baseline: CgA level presented as less than 5 × ULN *vs.* ≥ 5 × ULN	• Each factor assessed for importance using univariate Cox proportional-hazards model — Factors were potentially associated with PFS if the p-value was < 0.1

RECIST — Respond Evaluation Criteria in Solid Tumors ver. 1.1 (radiological response); DP — disease progression based on RECIST; BMI — body mass index; PS — performance status; ECOG — Eastern Cooperative Oncology Group; G1/G2 tumor cell differentiation G1 — well-differentiated, G2 — moderate differentiated; CgA — chromogranin A; ULN — upper limit normal; PFS — progression-free survival; OS — overall survival; *The ECOG performance status (PS) classifies the status of patients according to activities of daily living on a scale from 0 to 4, with 0 indicating that the patient is fully active

Results

Patient demographics and tumor characteristics

A total of 41 patients with sporadic, advanced pan-NET G1 (n = 13) and G2 (n = 28) were included in the analysis. The mean age of all patients was 55.4 ± 4.5 years (range 29–87 years) at the initial diagnosis. The vast majority were non-functioning pan-NET and only 3 patients (7%) had secretory tumors (2 gastrinoma and 1 malignant insulinoma). Baseline characteristics of the study population are shown in Table 2.

All patients were in advanced clinical stage (CS) CS III = 3 and CS IV = 38, 23 patients (56%) had a primary tumor ≥ 45mm; 32 patients (77.5%) had liver involvement, 30 patients (75%) had lymph node metastases, and 9 patients (32%) had bone metastases. In 18 patients, previous surgery was with intention to treat (ITT), including 11 subjects (61.1%) with R0 resection. Baseline pathological characteristics of tumors, previous history of surgery with intention to treat (ITT) for the overall group, and the subgroups of patients are presented in Table 3.

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

Median PFS for the entire cohort was 9.0 months (± 95% CI 4.7–24.0), number of events 37 (90.2%), OS was 105.4 months (± 95% CI 40.0–172.0), number of events 22 (54%). Details of PFS including events and censored cases are presented in Figure 2.

Subgroup analysis revealed that G1 tumors and no-bulky liver disease (< 25% liver involvement) were associated with significantly longer PFS; other parameters were not significant. Details including calculation of 2-year PFS and median PFS are presented in Table 4. The univariate analysis confirmed that tumor grade was associated with progression or death (G1 *vs.* G2; HR = 0.34, CI 95% 0.16–0.72, p = 0.005) and less than 25%, *vs.* ≥ 25%, of liver involvement HR = 0.31 (0.13—0.71, p = 0.01). In a multivariable model, functional (secretory) pan-NET was associated with shorter PFS (HR = 2.97, CI 95% 1.01–8.74, p = 0.048). At multivariate analysis, other covariates did not remain statistically significant. All results described above in detail are presented in Table 5. The summary of univariate analysis is presented graphically in Figure 3.

Clinical follow-up after initial treatments

After relapse following initial octreotide LAR therapy, patients received various treatment modalities including Radio-Ligand Therapy (RLT, previously PRRT using radiolabelled analogs of somatostatin receptor). The therapy was most commonly used as

Table 2. Baseline demographic and clinical characteristics for the overall group of patients

Variable	No. of patients (%)	Probability (p)
Age (years), mean, SD (range)	55.4 ± 4.5 (29–87)	
≤ 55	13 (32.0)	< 0.01
> 55	28 (68.0)	
Sex, n (%)		
Female	21 (51)	0.84
Male	20 (49)	
BMI, median (25–75% IQR)	25.2 (23.1–27.2)	
< 25	20 (49)	0.10
≥ 25	21 (51)	
Median time (months) from initial diagnosis (25–75% IQR)	3.0 (2.0–10.0)	0.23
Initial performance status (PS) n (%)		
ECOG = 0	11 (27.0)	0.26
ECOG = 1	23 (56.0)	
ECOG = 2	7 (17.0)	
Secretor tumors, n (%)		
Yes	3 (7.0)	< 0.001
No	38 (93.0)	
Initial CgA xULN, median (25–75% IQR)	2.0 (0.75–5.1)	
Initial CgA < 5 ULN	28 (6.0)	0.09
Initial CgA ≥ 5 ULN	10 (24.0)	
No data = 3	3 (7.0)	

The ECOG performance status (PS) classifies the status of patients according to activities of daily living on a scale from 0 to 4, with 0 indicating that the patient is fully active; SD — standard deviation; BMI — body mass index; IQR — interquartile range; ECOG — Eastern Cooperative Oncology Group; CgA — chromogranin A; ULN — upper limit normal

second-line treatment in 20 subjects (61%). Sunitinib and everolimus were used as a third-line treatment in 9 patients (50%). RLT/PRRT was introduced most commonly as fourth-line treatment followed by mTOR/TKI, capecitabine with temozolomide (CAPTEM), and combination of CAPTEM with PRRT in 20% of patients. The details of systemic therapies after relapse and disease progression after initial octreotide LAR therapy are presented in Figure 4.

Discussion

The results of this study suggest that octreotide LAR exhibits a moderate antiproliferative activity in pan-NET in terms of PFS. Subgroup analysis, as well as univariate and multivariate analyses, indicate that prolonged PFS may be associated with pan-NET G1 tumors and low metastatic liver burden of less than 25%, also in subjects with non-secretory pan-NET.

Progression-free survival

Prospective and retrospective clinical studies have revealed that the use of somatostatin analogs is associated with SD in 50–60% of GEP-NET patients, whereas PR based on RECIST rarely occur [5–10, 14, 15].

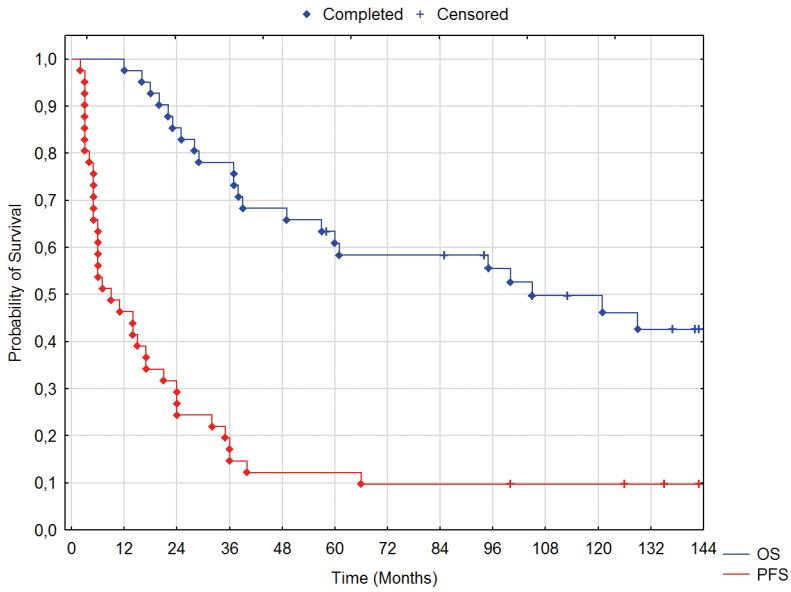
Although both retrospective and prospective studies in small patient groups had revealed the antitumor effect of these agents, the evidence of the antiproliferative effect of SSA came from the phase III randomized placebo-controlled double-blind study PROMID, involving 84 treatment-naive patients with disseminated well-differentiated NETs of midgut or unknown (possibly from midgut) origin [5].

In a similar retrospective analysis of 43 patients with pancreatic NET treated with octreotide LAR as first-line therapy — presented by Jann et al. [7] — median TTP was 13 months, which is similar to our results with median PFS in the whole group of patients in a range of 9.0 months (95% CI 4.7–24.0). A similar result was

Table 3. Baseline pathological characteristics of tumors, previous history of surgery with intention to treat (ITT) for the overall group and the subgroups of patients with pan-NET (n = 41)

Variable	Number of subjects (n = 41)	(%)
Grading (G), n (%)		
G1	13	(32.0)
G2	28	(68.0)
Grading based on Ki-67), n (%)		
G1 (Ki-67 < 3%)	13	(32.0)
G2 (Ki-67 = 3–9%)	17	(42.0)
G2 (Ki-67 = 10–20%)	11	(26.0)
Size of tumor, median (25–75% IQR)	47.5	(35.0-68.0)
< 45	18	(44)
≥ 45	23	(56)
Tumor status pT/cT* (initial)		
T1	1/1*	(5.0)
T2	4/4*	(20.0)
T3	12/10*	(54.0)
T4	1/8*	(24.0)
Lymph node status (initial)		
N-	11	(27.0)
N+	30	(73.0)
Liver involvement (initial)		
No	9	(22.5)
Yes	32	(77.5)
Liver involvement present before therapy (n = 37)		
< 25% (%)	28	(76.0)
≥ 25 % (%)	9	(24.0)
Presence of bone mts (before therapy)		
No	32	(78.0)
Yes	9	(32.0)
Previous surgery with ITT		
Yes	18	(44.0)
No	23	(56.0)
Radicality of surgical resection (n = 18)		
R0	11	(61.1)
R1	5	(27.8)
R2	2	(11.1)
Clinical stage (before start of therapy)		
III	3	(7.0)
IV	38	(93.0)

The ECOG/WHO performance status (PS) classifies the status of patients according to activities of daily living on a scale of 0 to 4, with 0 indicating that the patient is fully active; IQR — interquartile range; SD — standard deviation; PS — performance status; ITT — intention to treat; Ki-67 — proliferation index based on MIB1 — antibody; BMI — body mass index; IQR — interquartile range; ECOG — Eastern Cooperative Oncology Group; CgA — chromogranin A; ULN — upper limit normal; cT* — number of clinical evaluation of tumour stage, in somae cases the pathology were not obtained due to nonresectable tumours



OS at risk	41	41	35	32	28	25	23	23	19	16	14	12
Censored	0	0	0	0	1	0	0	3	1	2	0	3
Event	0	6	3	4	2	2	0	1	2	0	2	0
PFS at risk	41	19	13	8	5	5	4	4	4	3	2	2
Censored	0	0	0	0	0	0	0	0	1	0	1	2
Event	22	6	5	3	0	1	0	0	0	0	0	0

Figure 2. Kaplan-Meier plots of PFS 9.0 months (95% CI 4.7–24.0) and OS 105.4 months (95% CI 40.0–172.0) in all patients during follow-up. The data are presented for all patients who received at least three doses of Octreotide LAR therapy n = 41; PFS — progression-free survival; OS — overall survival

shown for median OS (98.0 months in the Jann study and 105.4 (95% CI 40.0–172.0) months in our study group). A nonsignificant difference was seen in PFS considering hormonal secretion between our results (p = 0.21) and Jann's report (p = 0.67) with median PFS of only 5.9 months in secretory tumors *vs.* 14.0 months in the non-secretory group, which could have been influenced by a small number of subjects with secretory tumors in our group [7]. Current studies support findings indicating that hormone overproduction does not influence PFS. However, in multivariate analysis secretory tumors were found to be associated with shorter PFS. Available data and our recent results suggest that PFS depends on tumor grading, initial PS, functionality of the tumor cells with hormone overproduction, liver involvement (lasting from 5.2 months in those with liver bulky disease to 32.1 months in those with NET G1).

Another retrospective analysis published by Laskaratos et al. [8] in a group of 254 subjects where 22 subjects with pancreatic NET had PFS 20 months (95%CI 12.079.0), seems to be overestimated compared to the results presented by Jann et al. [7] and our study.

Additional similarity was detected in median PFS in patients with NET G1 *vs.* G2 tumors, which favored patients with NET G1, and this was also indicated by previous reports [7–9, 16, 17]. The univariate analysis in our study indicated the association between tumor grade (G2) and liver bulky disease (≥ 25%) and faster progression or death. Although the multivariate model did not support these results and found that only functional status of pan-NET is associated with shorter PFS, the significance was borderline. Tumor grade and liver involvement status were relevant factors affecting therapeutic response. In previous studies — similarly to our results — a higher grade and more extensive liver involvement were related to shortened PFS [7, 8, 16–18]. Early-stage treatment with octreotide LAR significantly improved PFS but had no impact on OS [5, 19]. Analogs of SST were initially used for symptom suppression in functional GEP-NETs with hormonal overproduction

Table 4. Progression-free survival (PFS) in subgroups of patients based on some clinical, biochemical, and pathological parameters

Variable	N	2-year PFS (%)	Median PFS, months (95% CI)	p-value[a]
Age > 55	13	28	6.0 (4.9–17.0)	0.32
Age ≤ 55	28	31	14.0 (5.9–36.0)	
Male	20	35	17.0 (6.2–34.0)	0.59
Female	21	29	9.1 (5.2–14.8)	
BMI < 25	20	21	6.1 (4.9–14.1)	0.03*
BMI ≥ 25	21	41	17.1 (6.0–35.1)	
PS ECOG = 0	13	35	21.0 (5.2–42.6)	0.87 ^ 0.97 ^ ^
PS ECOG = 1	23	21	7.0 (5.0–17.0)	
PS ECOG = 2	5	16	6.0 (4.8–26.0)	
NET G1	13	56	32.1 (14.0–75.0)	
NET G2	28	18	5.9 (5.0–14.3)	0.01*
Size of tumor < 45	22	42	17.2 (6.0–35.4)	0.05
Size of tumor ≥ 45	19	19	6.2 (5.0–14.9)	
< 25% of liver volume involvement	28	47	21.1 (7.0–40.0)	0.01*
≥ 25% of liver volume involvement	9	8	5.2 (3.0–7.0)	
Bone metastasis (no)	34	34	14.0 (6.0–24.0)	
Bone metastasis (yes)	7	24	6.1 (5.0–21.0)	0.46
Secretory	6	16	5.9 (4.1–17.0)	0.21
Non-Secretory	35	34	14.0 (6.0–24.0)	
CgA < 5 × ULN§	28	40	14.1 (6.0–32.4)	0.054
CgA > 5 × ULN	11	17	6.1 (4.9–17.0)	

a — Cox-Mantel test; § — two patients had no initial CgA evaluation; *the significant difference between subgroups: BMI < 25 *vs.* BMI ≥ 25, NETG1 *vs.* NETG2, and < 25% liver volume involvement *vs.* ≥ 25% liver volume involvement; ^The difference between PS ECOG/WHO = 0 *vs.* PS ECOG/WHO = 1; ^^ The difference between PS ECOG/WHO=1 *vs.* PS ECOG/WHO = 2; PS — performance status; BMI — body mass index; ECOG — Eastern Cooperative Oncology Group; CgA — chromogranin A; ULN — upper limit normal

[5, 10, 20, 21]. This may reflect the unique tumor biology of NET [7–11,16–21]. Furthermore, most studies on the antineoplastic effects of octreotide LAR included populations with different primary sites, and it was difficult to compare the results of PFS and OS between our study and other reports [7–9, 17–22]; only a few retrospective studies and two small prospective studies in patients with gastrinoma had selected population of patients with pan-NET, who initially were treated using octreotide LAR [7, 8, 17, 20, 23].

Most authors agree that ORR of GEP-NET exposed to octreotide LAR is very low (approximately 5%). Both prospective and retrospective reports indicated ORR from 0 to 10%, with the latter one probably being an overestimation of response based on RECIST [5–9, 10, 15–18]. In the current analysis, details of ORR in our datasets were not included due to the focus on evaluation of the primary endpoints of the study.

The beneficial effects of octreotide LAR may also include OS. Patients from the PROMID trial were followed at least once a year until January 2013. In the Ki 67 < 10% subgroup, median OS was not reached in patients receiving octreotide LAR *vs.* 80.5 months in the placebo group (HR = 0.56, 95% CI 0.25–1.23; p = 0.14). In the HL > 10% subgroup, OS was 35 *vs.* 84 months (HR = 2.18, 95% CI 0.75–6.33; p = 0.14). The estimated HR of 0.56 in octreotide LAR-treated patients in the subgroup with low HL indicated a risk reduction of 44 % compared with placebo. This benefit was confirmed after 84.7 months of median follow-up [19]. Median OS of 105.4 months for our group of pancreatic NET is similar to what other authors have described (median OS — 98 months) in comparable populations of pNET [7, 17].

The univariate analysis performed in our study shows a significant difference in PFS in selected groups of our patients presented in Table 4 — some of the presented-above factors seem to have a role in shortening PFS, and additionally, these patients might be not optimal candidates for octreotide LAR as initial treatment.

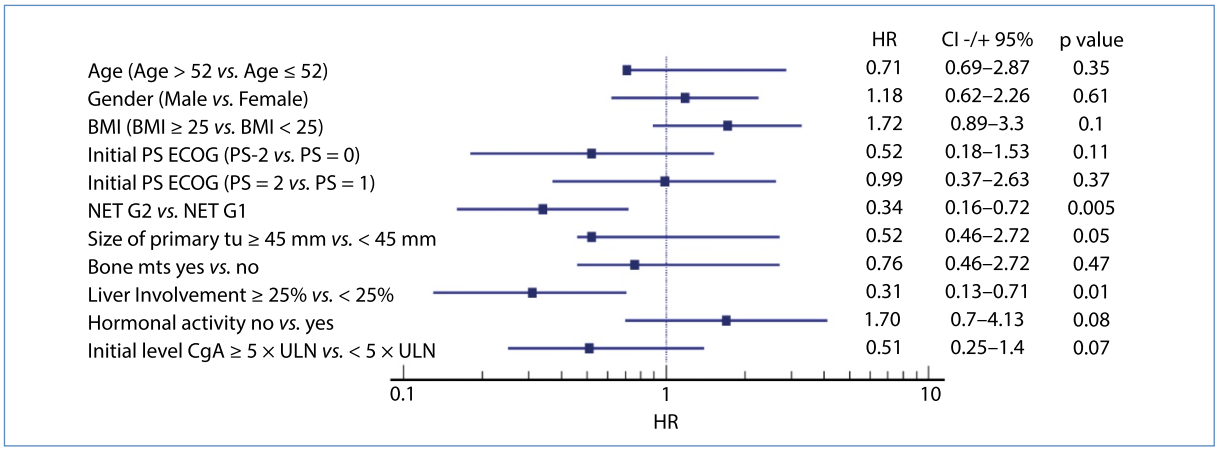


Figure 3. Graphical presentation of univariate analysis of model including age, sex; initial PS ECOG, cell differentiation (G), primary tumor size, bulky liver disease, BMI, presence of bone mts, CgA ratio over and below 5 × ULN, and secretion of the tumor with $p < 0.1$; CI — confidence interval; HR — hazard ratio; BMI — body mass index; PS — performance status; ECOG — Eastern Cooperative Oncology Group; NET — pancreatic neuroendocrine tumor; ULN — upper limit normal

Table 5. Analysis of covariates associated with progression-free survival (PFS)

	Univariate analysis			Multivariate analysis		
Variable	**HR**	**(95% CI)**	**p-value**	**HR**	**(95% CI)**	**p-value**
Age > 52	1.0	Reference				
Age ≤ 52	0.71	(0.69–2.87)	0.35			
Male	1.0	Reference				
Female	1.18	(0.62–2.26)	0.61			
BMI ≥ 25	1.00	Reference	1.35	0.59–3.10	0.48	
BMI < 25	1.72	(0.89–3.30)	0.1	1.00	Reference	
PS ECOG = 0	0.52	(0.18–1.53)	0.11			
PS ECOG = 1	0.99	(0.37–2.63)	0.37			
PS ECOG = 2	1.0	Reference				
NET G1	0.34	(0.16–0.72)	0.005*	0.43	0.13–1.42	0.17
NET G2	1.0	Reference	1.00	Reference		
Size of tumor < 45	0.52	(0.27–1.01)	0.05	0.72	0.27–187–	0.5
Size of tumor ≥ 45	1.0	Reference	1.00	Reference		
Bone mts no	0.76	(0.46–2.72)	0.47			
Bone mts yes	1.0	Reference				
< 25% of liver volume involvement	0.31	(0.13–0.71)	0.01*	0.51	0.18–1.51	0.23
≥ 25% of liver volume involvement	1.0	Reference	1.00	Reference		
Non-Secretory	1.00	Reference	1.00	Reference		
Secretory (functional)	1.7	(0.7–4.13)	0.08	2.97	1.01–8.74	0.048*
CgA ≥ 5 × ULN§	1.00	Reference		0.72	0.25–2.1	0.55
CgA < 5 × ULN	0.51	(0.25–1.4)	0.07	1.00	Reference	

BMI – body mass index; PS – performance status; ECOG – Easter Cooperative Oncology Group; CgA – chromogranin A; ULN – upper limit normal; *statistical significance

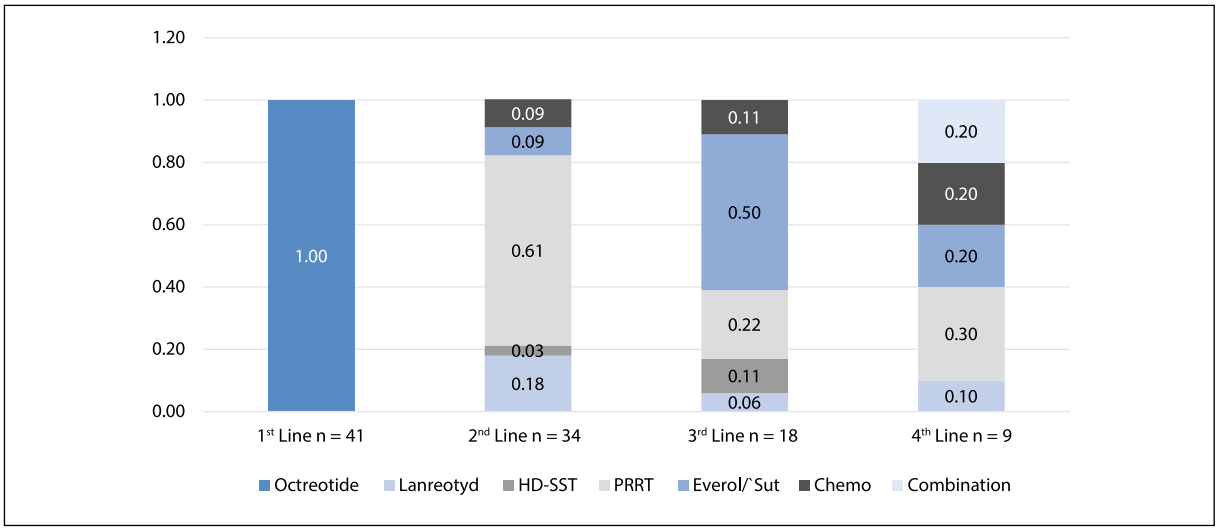


Figure 4. Types of systemic therapies after relapse and further disease progression of initial Octreotide LAR therapy presented as second-, third-, and fourth-line therapies; HD-SST — high dose of somatostatin analogs; Everol/Sut TKI — mTOR inhibitor/tyrosine-kinase inhibitor; PRRT — peptide receptor radionuclide therapy; Chemo — chemotherapy (CAPTEM) and Combination — PRRT + CAPTEM chemotherapy

Other reports indicated that tumor grade (G1 *vs.* G2) has an impact on PFS [7, 8, 13, 15, 19]. The Cox regression analysis in our study showed significantly different results between both groups (56.0 *vs.* 18.0 months) with HR = 0.34 for G1 *vs.* G2. The G2 pancreatic tumors less frequently responded to octreotide LAR therapy, which is in agreement with previous retrospective studies [7, 8] and small series prospective trials [20, 23].

Most patients in the PROMID study benefited from octreotide LAR 30 mg therapy although those patients with non-functioning NETs experienced the most benefit. On contrary, Shojamanesh et al. [20] in a small but homogeneous population with progressive malignant pancreatic gastrinoma (20 % of them had MEN1) found that octreotide was effective as an antineoplastic treatment in about 50% of the patients. The mean duration of response was approximately 25 months, which is different from our results of PFS in the group of secretor tumors [20].

However, even in patients with disseminated pancreatic NET and relatively poor prognosis (particularly G1 tumors), this type of therapy should be offered after initial diagnosis as previous reports indicated [7, 8, 17, 18, 20, 23].

In the pancreatic NET subgroup of the CLARINET study, 37% of patients had a hepatic tumor load over 25%, and 77% had received no previous treatment for NETs, which is less than in our study. We reported responses in 10 (27.8%) patients with bulky liver disease; in those with liver involvement, all had initial therapy using octreotide LAR [6].

Overall survival and follow-up treatments

Multiple therapeutical options in well-differentiated pan-NET G1 and G2 include somatostatin analogs, targeted therapies (sunitinib and everolimus), peptide receptor radionuclide therapy (PRRT — current name Radio-Ligad-Therapy), chemotherapy (CAPTEM) and combination of above-mentioned therapies. As options of treatment increase, potential sequencing alternatives grow exponentially making it difficult for clinical trials to explore each potential sequencing option [24]. Real-world data demonstrate patterns in clinical practice, outside of controlled environments of clinical trials. At present these data may help to improve clinical decision-making.

The National Cancer Institute's Neuroendocrine Tumor Committee recommended PFS as a primary endpoint for prolonged OS in patients with pan-NET excluding clinical trials with targeted therapies [25]. Imaoka et al. [26] performed an analysis in which PFS was significantly correlated with OS and could be a basis for further studies. Median OS for the entire group was 105.4 months. In contrast to other real-world data, RLT/PRRT therapy was most commonly used as second-line treatment in pan-NET, and targeted therapies were commonly used as third-line treatment [27]. PRRT/RLT was successfully implemented in patients with well-differentiated GEP-NET (especially SI-NET). The recently published retrospective analysis of efficacy (PFS) of PRRT/RLT in pan-NET indicated that this therapeutic approach reinforces the role of RLT in patients with advanced, somatostatin receptor-positive pan-NETs [28].

Limitations and strengths of the study

Several important limitations of this study need to be considered. Our retrospective study was relatively small (41 patients). It is well known that an estimate based on a small number of individuals is less reliable and when multivariate models are fitted to small data sets, the estimated impact of the covariates lacks precision to give reliable answers. This is also shown in our multivariate analysis, compared to univariate analysis based on the Cox proportional hazard rate model. In most of our selected covariates, we found at least 10 events for each covariate considered in building the model of the regression, so coefficients become unaffected by bias. In our dataset during follow-up, only 4 subjects had censored data, others had progression of all events or death. Due to the lack of a control group, there is a possibility of selection bias with regard to patients receiving first-line octreotide LAR therapy *vs.* patients treated with lanreotide Autogel 120 mg or other modalities. Also, there is some heterogeneity of cases, e.g. functional and non-functional, unknown dynamic of the disease before the start of therapy with octreotide LAR following initial diagnosis of pan-NET.

The major strengths of this study are the "real-world data" with a long follow-up. Moreover, our study provides further important clinical information on which group of sporadic pan-NET patients may benefit most from first-line treatment with octreotide LAR.

Conclusions

Based on our results we confirmed that octreotide LAR may be an effective antitumor therapy in patients with indolent disease, well-differentiated (G1) sporadic pan-NET with low tumor burden, less than 25% liver volume involvement. Further prospective and "real-world" studies are crucial to determine which patients will have an optimal benefit from somatostatin analogs.

Conflict of interest

All authors declare no conflicts of interest.

References

1. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008; 26(18): 3063– 3072, doi: 10.1200/JCO.2007.15.4377, indexed in Pubmed: 18565894.
2. Frilling A, Akerström G, Falconi M, et al. Neuroendocrine tumor disease: an evolving landscape. Endocr Relat Cancer. 2012; 19(5): R163–R185, doi: 10.1530/ERC-12-0024, indexed in Pubmed: 22645227.
3. Schimmack S, Svejda B, Lawrence B, et al. The diversity and commonalities of gastroenteropancreatic neuroendocrine tumors. Langenbecks Arch Surg. 2011; 396(3): 273–298, doi: 10.1007/s00423-011-0739-1, indexed in Pubmed: 21274559.
4. Astruc B, Marbach P, Bouterfa H, et al. Long-acting octreotide and prolonged-release lanreotide formulations have different pharmacokinetic profiles. J Clin Pharmacol. 2005; 45(7): 836–844, doi: 10.1177/0091270005277936, indexed in Pubmed: 15951474.
5. Rinke A, Müller HH, Schade-Brittinger C, et al. PROMID Study Group. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol. 2009; 27(28): 4656–4663, doi: 10.1200/JCO.2009.22.8510, indexed in Pubmed: 19704057.
6. Caplin ME, Pavel M, Ćwikła JB, et al. CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014; 371(3): 224–233, doi: 10.1056/NEJMoa1316158, indexed in Pubmed: 25014687.
7. Jann H, Denecke T, Koch M, et al. Impact of octreotide long-acting release on tumour growth control as a first-line treatment in neuroendocrine tumours of pancreatic origin. Neuroendocrinology. 2013; 98(2): 137–143, doi: 10.1159/000353785, indexed in Pubmed: 23797176.
8. Laskaratos FM, Walker M, Naik K, et al. Predictive factors of antiproliferative activity of octreotide LAR as first-line therapy for advanced neuroendocrine tumours. Br J Cancer. 2016; 115(11): 1321–1327, doi: 10.1038/bjc.2016.349, indexed in Pubmed: 27811856.
9. Arnold R, Trautmann ME, Creutzfeldt W, et al. Somatostatin analogue octreotide and inhibition of tumour growth in metastatic endocrine gastroenteropancreatic tumours. Gut. 1996; 38(3): 430–438, doi: 10.1136/gut.38.3.430, indexed in Pubmed: 8675099.
10. Toumpanakis C, Garland J, Marelli L, et al. Long-term results of patients with malignant carcinoid syndrome receiving octreotide LAR. Aliment Pharmacol Ther. 2009; 30(7): 733–740, doi: 10.1111/j.1365-2036.2009.04083.x, indexed in Pubmed: 19573169.
11. Strosberg JR, Yao JC, Bajetta E, et al. Efficacy of octreotide long-acting repeatable in neuroendocrine tumors: RADIANT-2 placebo arm post hoc analysis. Endocr Relat Cancer. 2015; 22(6): 933–940, doi: 10.1530/ERC-15-0314, indexed in Pubmed: 26373569.
12. Brierley JD, Gospodarowicz MK, Wittekind CT. TNM Classification of Malignant Tumours, 8th Edition. Wiley-Blackwell 2017.
13. Shanbhogue A, Karnad A, Prasad S. Tumor Response Evaluation in Oncology. J Comput Assist Tomogr. 2010; 34(4): 479–484, doi: 10.1097/rct.0b013e3181db2670.
14. Plöckinger U, Rindi G, Arnold R, et al. European Neuroendocrine Tumour Society. Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). Neuroendocrinology. 2004; 80(6): 394–424, doi: 10.1159/000085237, indexed in Pubmed: 15838182.
15. Baldelli R, Barnabei A, Rizza L, et al. Somatostatin analogs therapy in gastroenteropancreatic neuroendocrine tumors: current aspects and new perspectives. Front Endocrinol (Lausanne). 2014; 5: 7, doi: 10.3389/fendo.2014.00007, indexed in Pubmed: 24570674.
16. Panzuto F, Boninsegna L, Fazio N, et al. Metastatic and locally advanced pancreatic endocrine carcinomas: analysis of factors associated with disease progression. J Clin Oncol. 2011; 29(17): 2372–2377, doi: 10.1200/JCO.2010.33.0688, indexed in Pubmed: 21555696.
17. Butturini G, Bettini R, Missiaglia E, et al. Predictive factors of efficacy of the somatostatin analogue octreotide as first line therapy for advanced pancreatic endocrine carcinoma. Endocr Relat Cancer. 2006; 13(4): 1213–1221, doi: 10.1677/erc.1.01200, indexed in Pubmed: 17158766.
18. Aparicio T, Ducreux M, Baudin E, et al. Antitumour activity of somatostatin analogues in progressive metastatic neuroendocrine tumours. Eur J Cancer. 2001; 37(8): 1014–1019, doi: 10.1016/s0959-8049(01)00073-9.
19. Rinke A, Wittenberg M, Schade-Brittinger C, et al. PROMID Study Group. Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients with Metastatic Neuroendocrine Midgut Tumors (PROMID): Results of Long-Term Survival. Neuroendocrinology. 2017; 104(1): 26–32, doi: 10.1159/000443612, indexed in Pubmed: 26731483.
20. Shojamanesh H, Gibril F, Louie A, et al. Prospective study of the antitumor efficacy of long-term octreotide treatment in patients with progressive metastatic gastrinoma. Cancer. 2002; 94(2): 331–343, doi: 10.1002/cncr.10195, indexed in Pubmed: 11900219.
21. Grozinsky-Glasberg S, Shimon I, Korbonits M, et al. Somatostatin analogues in the control of neuroendocrine tumours: efficacy and mechanisms. Endocr Relat Cancer. 2008; 15(3): 701–720, doi: 10.1677/ERC-07-0288, indexed in Pubmed: 18524947.

22. Bartolomeo MDi, Bajetta E, Buzzoni R, et al. Clinical efficacy of octreotide in the treatment of metastatic neuroendocrine tumors: A study by the Italian Trials in Medical Oncology group. Cancer. 1996; 77(2): 402–408, doi: 10.1002/(sici)1097-0142(19960115)77:2<402::aid-cncr25>3.0.co;2-4.
23. Costa F, Gumz B. Octreotide A Review of its Use in Treating Neuroendocrine Tumours. Eur Endocrinol. 2014; 10(1): 70–74, doi: 10.17925/EE.2014.10.01.70, indexed in Pubmed: 29872467.
24. Megdanova-Chipeva VG, Lamarca A, Backen A, et al. Systemic Treatment Selection for Patients with Advanced Pancreatic Neuroendocrine Tumours (PanNETs). Cancers (Basel). 2020; 12(7), doi: 10.3390/cancers12071988, indexed in Pubmed: 32708210.
25. Kulke MH, Siu LL, Tepper JE, et al. Future directions in the treatment of neuroendocrine tumors: consensus report of the National Cancer Institute Neuroendocrine Tumor clinical trials planning meeting. J Clin Oncol. 2011; 29(7): 934–943, doi: 10.1200/JCO.2010.33.2056, indexed in Pubmed: 21263089.
26. Imaoka H, Sasaki M, Takahashi H, et al. Progression-free survival as a surrogate endpoint in advanced neuroendocrine neoplasms. Endocr Relat Cancer. 2017; 24(9): 475–483, doi: 10.1530/ERC-17-0197, indexed in Pubmed: 28684542.
27. Tsang ES, Loree JM, Speers C, et al. Sequence of therapy and survival in patients with advanced pancreatic neuroendocrine tumours. Curr Oncol. 2020; 27(4): 215–219, doi: 10.3747/co.27.5929, indexed in Pubmed: 32905342.
28. Clement D, Navalkissoor S, Srirajaskanthan R, et al. Efficacy and safety of LuDOTATATE in patients with advanced pancreatic neuroendocrine tumours: data from the NETTER-R international, retrospective study. Eur J Nucl Med Mol Imaging. 2022; 49(10): 3529–3537, doi: 10.1007/s00259-022-05771-3, indexed in Pubmed: 35389069.