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Evaluation of radiological and clinical efficacy of ^{90}Y-DOTATATE therapy in patients with progressive metastatic midgut neuroendocrine carcinomas

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Summary

Background: To evaluate the radiological and clinical therapeutic effectiveness of ^{90}Y-octreotate [DOTATATE] in patients with progressive somatostatin receptor–positive midgut neuroendocrine carcinomas (GEP-NETs).

Material/Methods: The study group: 34 patients, with histological proven extensive non-resectable and progressive midgut GEP-NETs. Radionuclide therapy (^{90}Y-DOTATATE) was given i.v. with a mean activity per administration 3,82 GBq. Initial clinical tumor responses were assessed 6–7 weeks after therapy completion and then once 3-monthly. The objective tumor response was classified according to the RECIST, initially between 4-6 months and then after each of the 6 months interval.

Results: At 6 months after treatment completion, radiological tumor response was observed in 6 subjects with PR (19%), 25 presented SD (78%) and single had PD (3%). Overall clinical response to therapy at 6 months follow-up was observed in 23 patients (68%), SD in 5 patients (15%) and PD in 6 (18%). A year after therapy radiological tumour response was seen in 11 patients (44%), SD had 12 subjects (44%) and DP was noted in 2 patients. Two years after completed therapy PR was seen in 6 patients (33%), SD in additional 11 subjects (61%), single patient had PD. Clinical response to treatment in terms of PR and SD were noted in 22 patients (88%) after 1 year and in 14 patients (87%) after 2 years. Median PFS was 20 months, while the median OS was 23 months. In the 6 patients with clinical PD within initial 6 months the median PFS was 6 months and OS 11 months, while in those with SD or PR PFS was 22 months and OS 26 months ($P<0.05$).

Conclusions: Therapy with ^{90}Y-DOTATATE is effective in terms of clinical response, however the radiological response measured by the RECIST criteria underestimates benefits of this type of therapy in patients with progressive somatostatin receptor–positive midgut neuroendocrine carcinomas.

Key words: **^{90}Y-DOTATATE therapy • midgut neuroendocrine carcinoma • RECIST**

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Background

Current therapeutic options for patients with progressive metastatic neuroendocrine carcinoma of gastroenteropancreatic origin (GEP-NETs) are limited. In those patients with midgut GEP-NET chemotherapy is not only toxic but also ineffective [1]. When a metastatic midgut neuroendocrine carcinoma is responsible for hormonal overproduction (i.e. carcinoid syndrome), treatment with conventional somatostatin analogues is method of choice in most of the cases, due to symptoms relief. However, the size of the tumor is reduced in very rare cases [2–4].

These limited approaches using standard oncological treatments in patients with progressive metastatic GEP-NETs have led towards the development of radionuclide tumor-targeting strategies [5–7]. The peptide radionuclide target therapy consists in the elimination of cancer cells using high energetic β-electrons, with lower toxicity to other normal tissues, due to direct binding [5,6,8]. The recommendation of the European Neuroendocrine Tumor Society (ENETS) is that targeted radionuclide treatment using somatostatin analogues should be considered in patients with midgut GEP-NET [9].

The previous data from used ^{90}Y [DOTATOC] indicates that this radionuclide treatment produces radiological partial response (PR) in a 10–35% patients [5,6].

Classical response evaluation in solid tumours (RECIST or WHO) uses radiological imaging approaches to measure changes of the tumour size before and after therapy. In these terms imaging requires a well-defined structural lesion which can be assessed and compared, if there is a reduction of tumour size during treatment as the basis for presumed clinical benefit [10]. However, with the development of new therapeutic strategies using for example peptide receptor radiotherapy (PRRT) classical structural radiological imaging could be inappropriate as neuroendocrine tumours would not significantly reduce in size after therapy as previous reports indicated [5,6,11–14].

This study represents clinical trial to report the efficacy ^{90}Y DOTATATE therapy after at least 6 months of follow-up period.

The Aim of this study

The aim of this study was to determine the radiological and clinical efficacy ^{90}Y DOTATATE therapy of disseminated midgut GEP-NET carcinomas eligible or appropriate for other forms of therapy.

Material and Methods

This was a prospective single site open-label study, approved by the Clinical Ethics Committee of the Central Clinical Hospital Ministry of Internal Affairs & Administration, where study was performed. Prior to the study's inclusion, written consent was obtained from all patients.

Patients

The study group comprised of 34 patients including 20 females, mean age 57 years (range 40–73 years). The inclusion criteria were as follows: histological diagnosis of midgut neuroendocrine carcinomas, WHO group 2 [9] with metastatic disease and evidence of clinical, biochemical (chromogranin A – CgA, 5HIAA) and/or imaging progression (CT or somatostatin receptor scintigraphy – SRS, with an increase of the size of tumor and/or increased number of lesions). This was assessed for a minimum period of 6 months prior to treatment.

Somatostatin receptor scintigraphy (SRS)

All patients were imaged with ^{99m}Tc-[HYNIC, Tyr^3]octreotide [HYNICTOC] with radiotracer avid lesions within the liver or any other part of the body having uptake at least or greater than normal liver, most within the abdomen and pelvis. The preparation of ^{99m}Tc-HYNICTOC before administration was described elsewhere [15,16]. Anterior and posterior whole body images, abdominal SPECT, including liver and any additionally required SPECT images were obtained 3–4 h after injection of 480–560 MBq of ^{99m}Tc-HYNICTOC.

Study parameters

None of the patients received prior treatment with other radiolabelled somatostatin analogues. In those patients receiving long acting somatostatin analogues i.m, the drugs were discontinued at least 4 weeks before radionuclide treatment, and re-introduced 3 to 4 days after therapy. Exclusion criteria were as follows: Hb <8 g/dl, WBC $<2\times10^3$/ml, platelets $<80\times10^3$/ml, creatinine level >1.2 mg/dL or GFR <30ml/min, and poor performance status (WHO – Zubrod status 3 and 4). Contraindications to treatment included: pregnancy, myelosuppression, and renal failure.

Preparation of radiotracer

Labeling

100 μg [DOTATATE] (DOTA-D-Phe^1-Tyr^3-octreotate) (piChem, Graz, Austria) with 50.0 mg ascorbic acid and 6.0 mg 5-dihydroxybenzoic acid were freeze-dried to form the kit. The kits were checked for sterility and bacterial endotoxines prior to use. The content of the kit was dissolved in not more than 0.5 ml ^{90}Y chloride (non carrier-added) in 0.05 M HCl (POLATOM, Poland) with the desired activity for treatment (max. activity per kit – 7.5 GBq ^{90}Y) and filled up to 1 ml with saline. The mixture was then incubated at 95°C for 25 min. After cooling down to room temperature the volume was adjusted to 2 ml with saline. Immediately before therapy the mixture was dissolved saline to final 50 ml.

Radiochemical purity (RCP) control

^{90}Y-DOTATATE was checked for RCP by analytical HPLC and SepPak C_{18}. All radiolabelled peptides showed a radiochemical purity of >99.0%, with no need for purification. The specific activities of radiolabelled peptide varied in the range 44.9–107.1 MBq/nmol (average 73.5±10.2 MBq/nmol).

Therapy – administration protocol

Ondansetron (GSK, UK) 8 mg was administered orally 30 min, before the start of i.v. infusion of amino acids

(Vamin 18, Fresenius-Kabi, Germany) 1500 ml, initiated by means of a slow i.v. injection, approximately 1.5–2 h before radiopharmaceutical administration. ^{90}Y-DOTATATE was administered via an injection pump system together with the amino acid infusion. The mean treatment activity 3.82 GBq was injected up to 20 min. The mean interval between therapies was 7 weeks (range 6–9 weeks). Patients were treated up to a cumulative activity of 11.2 GBq. Due to pure beta emission of ^{90}Y internal dosimetry was evaluated, based on previous reports considering ^{90}Y-DOTATOC treatment, which were performed using MIRD formalism. Using the cumulative dose mentioned above we expected similar radiation doses (bone marrow less then 2 Gy, and the radiation dose to the kidneys below 23 Gy) [17,18].

Biodistribution of the radiotracer

Before treatment each patient underwent standard somatostatin receptor scintigraphy (SRS) using ^{99m}Tc-HYNICTOC to show the uptake of the isotope. In the majority of disease sites the radioisotope activity was expected to be greater than physiological liver activity (Krenning score at least 2). In order to confirm that the therapeutic dose had a similar biodistribution, "Bremsstrahlung" images were acquired at 12-20 hours after the administration of ^{90}Y-DOTATATE using a dual head gamma camera (e-cam; Siemens) equipped with high energy collimation with a photopeak centered on 95 keV with a 50% window.

Safety and therapeutic effect

Patients were assessed clinically for general health and any tumor specific symptoms were recorded before treatment, 6 weeks after treatment and then at 3–6 monthly intervals. Routine hematology, liver and kidney function tests were measured before and then 10, and 20 days after each therapy session. Hormone levels in case of secretory tumors and chromogranin A (CgA) were measured before the start of therapy, 6 weeks after completion of the last cycle of therapy followed at 3 monthly intervals thereafter. A WHO Performance Status was estimated in each case before the beginning of therapy and 6 weeks after the completion of therapy. Improvement of clinical symptoms was assessed as clinical benefits, but not as an objective response.

Assessment of Effectiveness

The radiological response to therapy (RECIST)

Tumors on CT scans were measured and scored, according to the RECIST [4]. All patients were subjected to a three phase contrast enhanced spiral multidetector CT (Aquilion 16, Toshiba), and 1 mm slices within the 2 months prior to the first therapy. Post-therapeutic imaging was performed after 4–6 months of follow-up. The CT images were interpreted and measured using a dedicated workstation (Vitrea™, Toshiba), with total freedom for window and level adjustments, and for the magnification of each image at the time of analysis. Every tumor was measured in single maximal dimensions in the transverse plane and its largest perpendicular diameter on the same image. Pre and post therapy CT images were compare to each other together to make diagnosis of potential changes more certain

Biological tumor response

The biological tumor response was determined by means of serial measurements of plasma chromogranin-A (CgA), 24-hour urinary 5-hydroxyindole acetic acid (5-HIAA). Results were obtained at pre-treatment, 6-8 weeks post therapy and then at 3 monthly intervals.

Clinical response and performance status

The patients were assessed for clinical responses by completing a self-assessment questionnaire, and during physician directed interviews conducted before the beginning of treatment and 4–6 weeks following each treatment cycle. The items they assessed included appetite, malaise, weight loss, and the presence and intensity and frequency of abdominal pain, diarrhea, flushing, nausea, vomiting, fever, wheezing, and abdominal bloating. Any analgesic and somatostatin analogue requirements before and after treatment were recorded. The patients' clinical stage was assessed before and 6 weeks after completed therapy using standard WHO status.

Statistical analysis

Overall survival (OS) and progression free survival (PFS) were evaluated using Kaplan-Meier's method. Comparison of OS and PFS between different groups of patients were assessed using the Cox-Mantel test. Differences in WHO status in patients before therapy and after completed radionuclide therapy were performed using Wilcoxon's Matched Pairs Test. $P<0.05$ was considered as statistically significant.

Results

Of the 34 patients treated, 5 had as initial diagnosis small midgut tumour base on recent WHO classification of GEP-NET pathology, as pT2, 10 had pT3 and 19 had initial pT4 tumour [19]. Summarized clinical data of treated patients are presented on [Table 1], including initial WHO performing status, pathological and clinical initial tumor staging, previous systemic therapy, for all subjects and those with secretor and non-secretor tumour.

A total of 100 therapies were performed with mean administered activity of 11,2 GBq (range 4.1–16.2 GBq) per patient (mean 3.82 GBq per therapy), most of them 24 subjects had 3 times and 4 patients had 4 and next 6 two therapy sessions. The biodistribution of the ^{90}Y-DOTATATE was seen in the "Bremsstrahlung" images and in most cases perfectly matched the diagnostic ^{99m}Tc-HYNICTOC image performed before therapy.

Toxicity

No major sudden acute adverse events were recorded either during the therapy session or within 24 h of ^{90}Y-DOTATATE therapy. Mild nausea and vomiting, (probably due to the co-administration of amino acid infusion) were the only adverse events. Those effects disappear spontaneously within 6 h, after discontinuation of the AA infusion.

Table 1. Patients characteristics, including clinical data, type of therapy and secretory and non secretory cancers (n=34 subjects with midgut GEP-NET, WHO group 2).

Characteristics	All		Non-Secretor		Secretor	
	No	percent	No	percent	No	percent
No of patients	34	100	13	38	21	62
Age						
Mean age	57		54.8		58.3	
Range	40–73		40–69		48–73	
Sex						
Female	20	53	9	69	11	52
Male	14	47	4	31	10	48
Initial Performance Status						
WHO status=1	22	65	12	92	10	48
WHO status=2	12	35	1	8	11	52
Presence of Primary Tumour	14	41	4	31	10	48
Previous Chemotherapy	21	62	10	77	11	52
Previous Analogues SSTR	15	44	4	13	10	48
Liver Involvement	28	82	10	77	18	86
Other Sides of Mts	8	24	3	23	5	38
SRS (Krenning uptake score)						
4	23	68	8	62	15	62
3	11	32	5	38	6	38

Therapeutic effect

Radiological (RECIST) tumor response data was available in 32 patients who completed at least two or more cycles of therapy. In the remaining 2 cases patient died after their second cycle of treatment before a radiological response could be assessed. On CT imaging performed 4–6 months after the last cycle therapy 6 cases (19%) had a substantial reduction of tumor size, as partial response (PR), 25 patients (78%) were defined as disease stability (SD). A one year after the completion of treatment, radiological tumor response was evaluated in 25 patients. In 11 subjects (44%) had PR (Figure 1A–C), 2 patients (8%) had disease progression, due to continuous tumor growth, others 12 patients had SD (48%). A two years after PRRT radiological tumor response was evaluated in 18 patients, 6 of them still had PR (33%), 11 subjects had SD (61%) and single had PD (6%). Details of radiological tumor response including all subjects and those with secretor and non secretor cancers is presented on (Table 2). Graphical presentation changes of max LD base on RECIST in all patients after 6, 12 and 24 months of clinical follow-up is shown as waterfall charts on (Figure 2A–C).

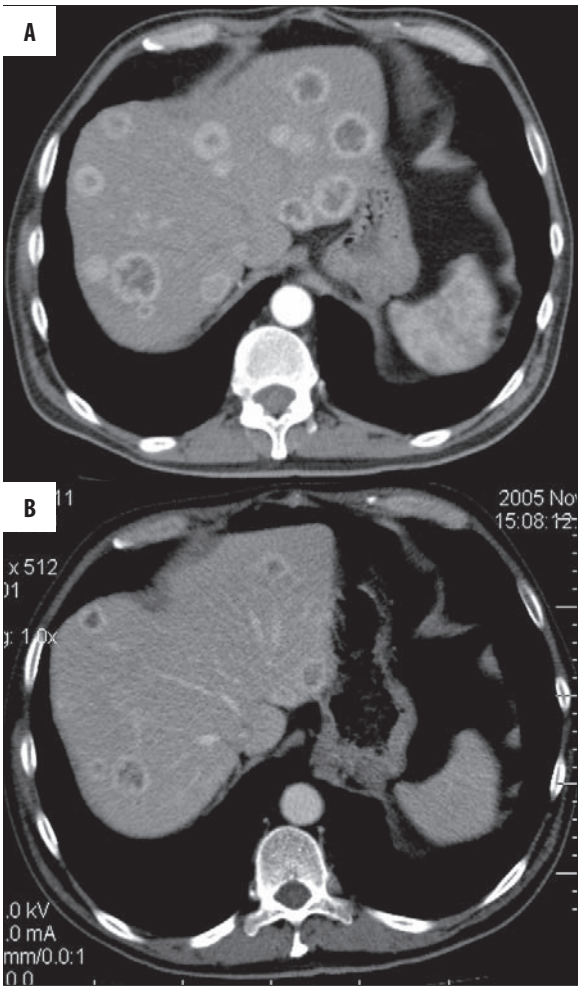
Clinical response

Carcinoid syndrome with dominant diarrhoea (bowel movements more than three times a day) was reported in 19 patients before therapy in more than half of the cases (53%) cases there was reduction of diarrhoea, and additional in 4 cases bowel movements back to normal. Minor relief in the frequency of bowel motility was noticed in 9 patients. Second characteristic sign of the carcinoid syndrome a flushing was reported in 15 subjects pre-therapy with significant reduction after therapy in 9 of them. Abdominal pain was reported in 16 patients before ^{90}Y-DOTATATE therapy, 12 of them noted a reduction of pain, a during therapy and most of them 4-8 weeks after therapy, with a reduction in analgesic and other medication administration.

Before therapy WHO status 1 noted in 22 cases (65%) WHO status 2 noted in 12 cases (35%). After therapy WHO status 0 noted in 3 cases (10%), WHO status 1 in 26 cases (80%) and WHO 2 in 4 cases ($P<0.05$). Details of clinical response presented on (Table 2).

PFS and OS

In this population of patients median PFS was 20 months (±95%CI 16–22.4); median OS was 23 months (±95%CI 19.1–26.6) (Figure 3). In those 6 patients with early disease progression the median PFS was 6 months, and OS 11 months. There was no significant differences of PFS and OS between group of patients with secretor and non-secretor midgut cancers ($P>0.05$). Survival rate at 2 years was 78% for all patients and 80% in those with non-secretor midgut cancer and 75% in those with secretor midgut tumours.



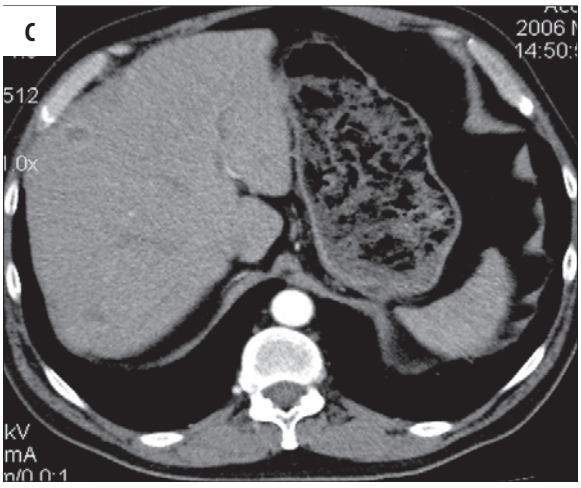


Figure 1. A 58 years old male with clinically carcinoid syndrome, histology – NECLM (midgut carcinoid, WHO group 2). (**A**) Standard CT scan after i.v. contrast enhancement (portal-venous phase), before ^{90}Y DOTATATE treatment; (**B**) CT scan, 6 months after completed radionuclide therapy, RECIST – PR. Clinically almost no symptoms of carcinoid syndrome; (**C**) 12 months after completed therapy, RECIST – PR.

Discussion

Patients with midgut neuroendocrine cancers often present with advanced disease, with non-resectable tumor deposits and complete cure of these patients is limited. In these cases only palliation can be offered [1,9].

The use of radionuclide target (labelled somatostatin analogues) therapy to deliver a high energetic β emitter into tumor tissues has been developed over the past 8 years [17–18]. Current European Neuroendocrine Tumor Society (ENETS) recommendations indicated use of radiolabelled somatostatin analogues in patients with midgut GEP-NET (WHO group 2).

This type of therapy with targeted mechanisms of action, have demonstrated significant limitation and unsuitability in terms of structural tumor evaluation that measure only size of the lesions like standard RECIST or WHO classification do. Single or bi-dimensional evaluation of tumour size reduction after therapy currently changes the paradigm of tumour response. Our results show the discrepancy between radiological and clinical response on ^{90}Y-DOTATATE therapy. This refers to PR estimated by radiological and clinical criteria, which is especially seen after 6 months after therapy completion: 19% vs 68%. This was less evident during the follow-up period: 44% vs 64% at 12 months and 33% vs 39% at 24 months. These results are similar to those presented in others reports, consider first 6 months of follow-up, which indicated relatively low rate of radiological responses of 22–34% during first 6 months of follow-up [5,6,17,18].

In fact significant number of patients had disease stabilization as radiological response, which could be correlated as some kind of benefits in group of patients with extensive progressive cancer. Stable disease in our study seems to be higher then others reports, which indicated an objective response about 60–65% rate. The explanation of these results could be attributed to the different peptide used by others described in majority reports [5,6,17,18,20]. In our study [DOTATATE] analogues was used, with higher affinity towards SST2 receptors, which have potentially better efficacy during therapy. There are few reports using this peptide labelled with ^{177}Lu, ^{90}Y, or mix of both radioisotopes [11,13,21,22] in patients with advanced GEP-NET. Radiological disease stability was seen in 76% and PR was seen in 17% of cases, these results perfectly mach in our rate with SD 78% and PR 19%.

Objective radiological response evaluation is important to assess the treatment efficacy of any anticancer drugs. Some kind of standardisations of imaging results is very important to compare different type of therapy, or different anticancer drugs, because clinical evaluation could be subjective. It is generally accepted that a decrease in tumor size correlated with treatment effect [23,24].

As mentioned before, in terms of objective response to therapy using RECIST or WHO criteria there is some criticism, due to non-adequate discrimination of the real benefits of therapy. Common sense would be to use other criteria, such as time to progression or overall survival, considering treatment efficacy [24]. The common clinical problem in extensive neuroendocrine carcinomas is connected

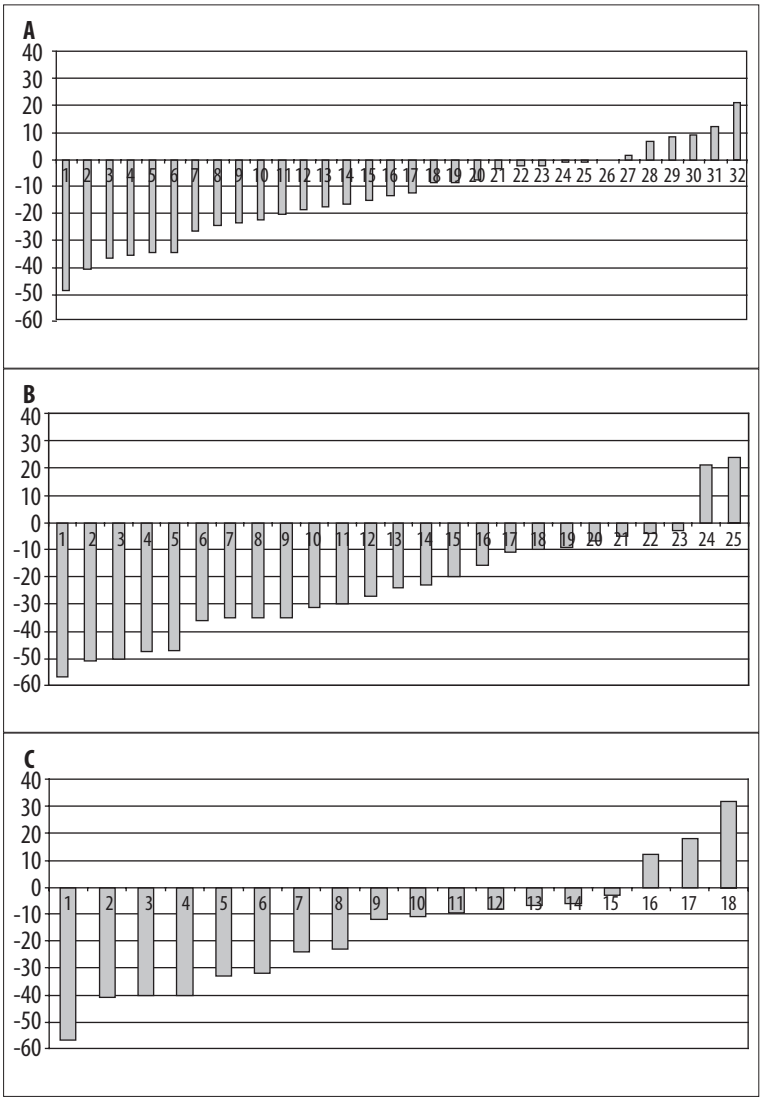


Figure 2. Changes of tumour and/or metastasis lesions size (max LD base on RECIST) in all patients with midgut GEP-NET treated ^{90}Y-DOATATE during clinical follow-up. A. After 6 months (N=32), B. After 12 months (N=25) and C after 24 months (N=18).

Table 2. Comparison of radiological response (RECIST) and clinical response in group of 34 patients with midgut GEP-NET.

Time of follow-up	RECIST		Time of follow-up	Clinical	
	No	Percent		No	Percent
6 Months (N=32)			6 Months (N=34)		
PR	6	19	PR	23	68
SD	25	78	SD	5	14
PD	1	3	PD	6	18
12 Months (N=25)			12 Months (N=25)		
PR	11	44	PR	16	64
SD	12	48	SD	6	24
PD	2	8	PD	3	12
24 Months (N=18)			24 Months (N=18)		
PR	6	33	PR	7	39
SD	11	61	SD	9	50
PD	1	6	PD	2	11

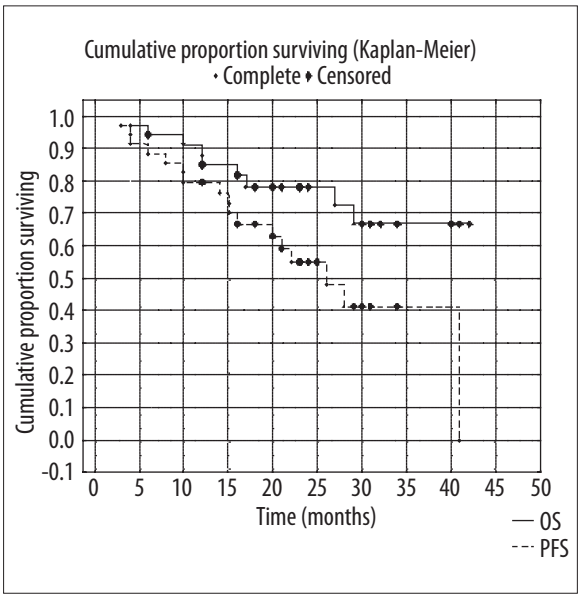


Figure 3. Kaplan-Meier curve of PFS and OS midgut GEP-NET patients treated ^{90}Y-DOTATATE.

with therapeutic benefit although without tumor regression, observed after target radionuclide therapy. Additional it seems to be that complete or partial responses using RECIST or WHO cannot be the adequate end points of any current targeted clinical trials. In some cases, overall survival, progression-free survival or disease control could be more adequate end point of the study than RECIST or WHO criteria of target therapy efficacy. OS and PFS in our group of patients during clinical follow-up had similar rate as presented by others long terms efficacy those by Kwekkeboom et al. [13], and Baum et al. [22]. The number of patients in this study was relatively small, which is some kind of limitation. Except for 2 studies mentioned above [13,22] which enrolled over 300 patients, most presented data comprising less than 100 patients [5,6,11,20]. However, neuroendocrine tumours are relatively rare, there is no possibility to match with a control group for statistical comparison or randomized the study. In our study we tried to compare patients with secretory and non-secretory carcinomas, with no significant difference between groups, considering OS or PFS, which indicated that secretory and non-secretory cancer patients presented a similar natural history.

Using RECIST or WHO response criteria we are aware other limitation of structural measurement alone in potential tumour reduction after therapy [23]. It could be related to often ill-defined and confluent metastatic lesions, which could provide different tumour margins definition. Additional if there is multiple metastatic deposits the selection of target lesions and again measurements of them after therapy, could be source of differences in real response [23,25]. To avoid these limitation in our study all images and evaluation of tumour response was done by single radiologist (A.S), who read images before and after therapy the same time. More precisely will be measurement all cancer deposits, due to differences in treatment response in different lesions, but it will be impractical and in some cases impossible.

The future of tumour response evaluation, using structural imaging, could be made to measure tumor volume, base on widespread multidetector CT, or MR imaging, and post-image processing procedures to evaluation of the real longest diameter of a lesion [26].

Conclusions

- Intravenous therapy using ^{90}Y-DOTATATE is effective palliative treatment method for patients with progressive extensive somatostatin receptor–positive midgut GEP-NET.
- The objective radiological response and clinical response, is comparable with previous data considering.
- Further investigations using structural and functional imaging approaches should be used to more precisely assess tumour response on ^{90}Y-DOTATATE therapy, particular within first 6 months after therapy.

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