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Peritoneal Carcinomatosis in Gastro-Entero-Pancreatic Neuroendocrine Neoplasms: Clinical Impact and Effectiveness of the Available Therapeutic Options

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Keywords

Peritoneal carcinomatosis · Neuroendocrine neoplasms · Bowel obstruction · Peptide receptor radionuclide therapy · Disease control

Abstract

Background: Peritoneal carcinomatosis (PC) can affect the quality of life of patients with gastro-entero-pancreatic neuroendocrine neoplasms (GEP-NENs). Peritoneal disease control by medical therapies in these patients has been poorly investigated ***Objectives:*** To describe, in a consecutive series of GEP-NENs, the clinical impact of PC and to report the effectiveness of available treatments in PC control. ***Methods:*** A retrospective, monocenter analysis was performed of 135 GEP-NENs (1993–2016) with at least a 12-month follow-up. Peritoneal disease progression was defined as detection of a significant increase in size or appearance of new implants by imaging. ***Results:*** A total of 62.9% of cases had diffuse PC (involving at least 2 abdominal quadrants). According to WHO 2017 classification, cases were 42.3% neuroendocrine tumors NET-G1, 45.5% NET-G2, 6.5% NET-G3, 4.9% neuroendocrine carcinomas NEC-G3, and 0.8% mixed neuroendocrine-nonneuroendocrine neoplasms. Bowel obstruction occurred in 30 (22.2%) patients mainly depending on size of peritoneal implants (HR: 1.10; 95% CI: 1.02–1.20; $p = 0.01$). Patients with diffuse PC treated with peptide receptor radionuclide therapy (PRRT) showed peritoneal progression in 37.5% of cases, and bowel obstruction or ascites in 28.1%. Better peritoneal disease control was observed in cases receiving somatostatin analogs at first-line therapy, probably due to a less aggressive disease behavior for these patients. ***Conclusions:*** Bowel obstruction is not uncommon in GEP-NENs with PC. PRRT should be adopted with caution in GEP-NENs with diffuse PC, but larger series are needed to confirm these data.

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Introduction

Peritoneal carcinomatosis (PC) affects 6–30% of gastro-entero-pancreatic neuroendocrine neoplasms (GEP-NENs). Although it frequently represents an occasional finding during disease staging or follow-up, in some patients it can instead negatively influence quality of life, with deterioration of clinical status. PC can indeed cause recurrent abdominal pain or even bowel obstruction, with bloating, nausea, and vomiting as additional clinical presentation and need of surgery in a subgroup of patients [1–3].

Most of the studies published on GEP-NENs with PC are surgical series [4–10], proposing classifications aimed to predict patients' prognosis according to disease extent. However, only a minority of patients with PC are resectable, and the impact of systemic medical therapies both on peritoneal disease progression (DP) and PC-related clinical complications still needs to be clarified [11].

The aims of this study were to describe the clinical impact of PC in GEP-NENs and to report the effectiveness of available therapies in controlling peritoneal disease.

Materials and Methods

Patient Selection and Data Collection

This monocenter retrospective analysis of a histological and clinical database included all patients with the following criteria: (1) histological diagnosis (1993–2016) of sporadic GEP-NENs; (2) PC finding at surgery and/or at least 2 imaging tests; (3) a minimum of 12-month follow-up after PC detection for alive patients. Exclusion criteria were: unknown or non-GEP primary site, a follow-up shorter than 1 year, or genetic syndromes (i.e., type I multiple endocrine neoplasia, von Hippel-Lindau syndrome).

PC diagnosis was considered as the "starting point" for clinical data collection and outcome assessment. Data were retrieved from patients' charts and diagnostic reports. GEP-NENs were classified according to the European Neuroendocrine Tumor Society (ENETS) TNM grading system [12, 13]. The WHO 2017 classification [14] was applied also to the non-pancreatic cases (after histopathological revision).

Clinical management was discussed at interdisciplinary tumor board meetings, according to suggestions of the ENETS Guidelines [15–20]. Follow-up programs were personalized according to tumor biology, disease status, and ongoing treatments, including: computed tomography (CT), magnetic resonance imaging, functional imaging tests such as ^{111}In-Octreoscan®, ^{68}Ga-DOTATOC positron emission tomography/CT (^{68}Ga-DOTATOC PET/CT), or ^{18}fluorodeoxyglucose-PET/CT (^{18}FDG-PET/CT). Imaging tests performed at other centers were reassessed at our site by our experienced radiologist (T.D.) and nuclear medicine specialist (V.P.). Only a proportion of patients received surgery, thus the proposed PC classifications [11] could not be applied to all patients. Peritoneal disease was defined as "focal" when described only as histological infiltration of the peritoneal serosa without any macroscopic lesions [6]. For others, when the PC was found to involve at least 2 abdominal quadrants (on surgery and/or imaging), or it was classified as "diffuse." If PC was limited to 1 quadrant it was termed as "localized."

Bowel obstruction was defined as clinical (i.e., abdominal distention, nausea, vomiting, bloating, abdominal pain) and radiological evidence of intestinal obstruction associated with PC by surgical findings or peritoneal DP at imaging tests [21]. Peritoneal DP was defined as imaging description of new implants or an increase in their size according to the RECIST 1.1 criteria [22]: solid nodules qualifying as measurable target lesions with an increase of at least 5 mm and 20% of longest diameter, and non-measurable non-target lesions implants (e.g., smaller than 1 cm, diffuse peritoneal thickening, or omental caking) subjectively assessed as recommended. Peritoneal progression-free survival (PFS) was expressed as the time between PC diagnosis and the date of peritoneal DP. Peritoneal recurrence-free survival (RFS) instead represented the time between peritonectomy and the date of assessment of peritoneal recurrence. General disease status including non-peritoneal disease was also assessed according to the RECIST 1.1 criteria [22].

Table 1. Patients' presentation at PC diagnosis: demographic, clinical, and pathological features (n = 135)

Male gender	64 (47.4)
Age, years	59 (25–86)
Tumor primary site	
Small bowel	92 (68.2)
Pancreas	18 (13.3)
Other gastrointestinal sites	25 (18.5)
Carcinoid syndrome	42 (31.1)
Ki67[a], %	4 (1–80)
WHO classification[a]	
NET-G1	52 (42.3)
NET-G2	56 (45.5)
NET-G3	8 (6.5)
NEC-G3	6 (4.9)
MiNEN	1 (0.8)
Resection of primary tumor	105 (77.7)
PC since NEN first diagnosis	81 (60.0)
Time from NEN diagnosis to PC detection, months	30 (1–179)
Other metastatic sites	104 (77.0)
Only intra-abdominal	85
Extra-abdominal	19
Focal PC	16 (11.8)
Size of peritoneal implants[b], mm	12 (4–35)
Diffuse PC[c]	85 (62.9)

Data are presented as n (%) or median (range), as appropriate. WHO classification according to WHO 2017 [14]. PC, peritoneal carcinomatosis; WHO, World Health Organization; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; MiNEN, mixed neuroendocrine-nonneuroendocrine neoplasm; NEN, neuroendocrine neoplasm. [a] Available in 123 patients. [b] Available in 49 patients. [c] PC involving at least 2 abdominal quadrants.

Table 2. PRRT and peritoneal carcinomatosis: patients' presentation at PRRT start and response to therapy

No.	Primary site	Other metastases	Ki67, %	PC extent	Time to PRRT, months	Therapy line[a]	PRRT details	Peritoneal DP after PRRT	Clinical complications after PRRT
1	small bowel	liver	1	diffuse	6	2	Lu (4 cycles)	no	
2	small bowel		1	diffuse	68	4	Lu (3 cycles)	no	
3	small bowel	liver	2	diffuse	43	3	Lu (3 cycles)	no	
4	small bowel	liver	8	diffuse	16	2	Y (1 cycle)	yes	bowel obstruction
5	small bowel	chest lymph nodes	8	diffuse	28	3	Lu (1 cycle)	yes	
6	small bowel		2	diffuse	46	2	Y (2 cycles)	no	
7	small bowel	liver, pancreas	5	diffuse	73	2	Lu (1 cycle)	no	
8	small bowel		1	diffuse	3	1	Lu (1 cycle)	yes	ascites, bowel obstruction, death
9	small bowel	liver, pancreas	3	diffuse	4	1	Y (1 cycle)	no	
10	appendix		5	localized	8	2	Lu (2 cycles)	no	
11	colon	chest lymph nodes, liver, bones	3	diffuse	24	2	Lu (2 cycles)	no	
12	pancreas	liver	16	diffuse	46	4	Lu (3 cycles)	no	
13	small bowel	liver	2	localized	26	2	Lu (2 cycles)	no	
14	small bowel	liver	5	diffuse	37	2	Y (3 cycles)	yes	bowel obstruction
15	stomach	liver	20	localized	31	2	Y (2 cycles), Lu (1 cycle)	no	
16	small bowel	liver	1	diffuse	6	2	Y (2 cycles)	no	
17	stomach	liver	20	diffuse	66	4	Lu (1 cycle)	yes	ascites, bowel obstruction
18	rectum	liver, lung	unknown	diffuse	12	1	Y (2 cycles)	no	
19	pancreas	liver	2	diffuse	14	3	Lu (3 cycles)	yes	Ascites
20	small bowel	liver	12.5	localized	7	3	Y (1 cycle)	no	
21	small bowel	liver	1	diffuse	148	3	Y (1 cycle)	no	
22	small bowel	liver	2	diffuse	34	2	Lu (2 cycles)	yes	ascites, bowel obstruction
23	stomach	chest lymph nodes, liver, pancreas	15	localized	2	1	Y (2 cycles), Lu (2 cycles)	no	
24	small bowel		2	diffuse	9	1	Y (1 cycle)	yes	
25	rectum	liver, bones	15	diffuse	2	1	Lu (3 cycles)	no	
26	small bowel	liver	2	diffuse	45	2	Y (1 cycle)	yes	ascites
27	small bowel	liver	5	diffuse	15	2	Lu (4 cycles)	no	
28	small bowel	liver, bones, lung, pericardium	2	diffuse	88	3	Y (3 cycles)	yes	bowel obstruction
29	small bowel	liver	2	diffuse	6	2	Lu (4 cycles)	no	
30	small bowel	liver, bones	1	diffuse	5	1	Y (3 cycles)	no	
31	small bowel		35	diffuse	41	2	Lu (3 cycles)	yes	bowel obstruction
32	stomach	liver	60	diffuse	13	1	Lu (3 cycles)	yes	

PRRT, peptide receptor radionuclide therapy; PC, peritoneal carcinomatosis; DCR, disease control rate; DP, disease progression; Y, Yttrium; Lu, Lutetium. [a] Therapy line for peritoneal disease.

Statistical Analysis

Statistical analysis was performed with MedCalc® software (www.medcalc.be; version 15.6.1). The distribution of continuous variables was presented as median and range. Survival analysis was performed by the Kaplan-Meier method or log-rank test. Risk factor analysis was developed following the Cox regression hazard models. Results were expressed as hazard ratio (HR), together with 95% confidence interval (CI). Statistical significance was indicated by a p value <0.05.

Results

Patient Features

Out of 472 patients with histological diagnosis of advanced sporadic GEP-NENs (1996–2016) and with available data on follow-up, 135 (28.6%) fulfilled the inclusion criteria (features detailed in Table 1). All functioning tumors presented with a carcinoid syndrome, and all had a small bowel primary site apart from 2 pancreatic cases. None of these patients suffered from Hedinger syndrome.

Histological features derived from surgery of the primary tumor site in 23 (17.1%) cases, from PC evaluated at surgery in 65 (48.1%), while in 47 patients (34.8%) histological description was related to other metastases (15 surgical samples, 32 biopsies). Two well-differentiated G3 cases had histologically progressed from a G2 histology at the initial tumor diagnosis, and 5 G2 cases had progressed from an initial G1 histology.

The first PC detection was due to conventional imaging tests in 57 (42.3%) patients, functional imaging tests in 13 (9.6%), and surgery in 65 (48.1%). Sixty-six patients (48.8%) had received at least 1 therapy line before PC diagnosis (range: 1–4): surgery in 58 cases (44 of which were resection of tumor primary site), hepatic locoregional treatment in 4 patients, 17 were already on somatostatin analogs (SSAs) either alone or in combination with interferon (in 3 cases), peptide receptor radionuclide therapy (PRRT) was adopted in 4 patients, chemotherapy (CHT) in 10, and 1 patient had received everolimus. Median follow-up after PC diagnosis was 48 months (range: 12–224).

Clinical Complications

Fifty-eight (42.9%) patients complained of recurrent abdominal pain, while PC-related intestinal obstruction occurred in 30 (22.2%) patients after a median time of 16 months from PC diagnosis (range: 1–64). Fifteen cases required surgery, and 2 more than once.

While in 23/135 (17%) cases bowel obstruction could not be related to the current therapy, it was observed during PRRT in 7 out of the 32 (21.9%) subjects receiving this treatment and affected by diffuse PC (Table 2).

Univariate analysis revealed Ki67, size of peritoneal implants, and diffuse form of PC as risk factors for bowel obstruction due to PC (Table 3). However, on multivariate analysis, only size of peritoneal implants as continuous variable was confirmed as a significant risk factor for bowel obstruction (HR: 1.10, 95% CI: 1.02–1.20; $p = 0.01$).

Table 3. Occurrence of bowel obstruction in GEP-NENs with peritoneal carcinomatosis: risk factor analysis

Variables	HR	95% CI	*p*
Univariate analysis			
Gender (male)	1.01	0.49–2.06	0.98
Age[a] (years)	1.02	0.99–1.06	0.17
Small bowel (primary site)	1.20	0.52–2.80	0.67
Primary tumor size[a] (mm)	1.01	0.99–1.03	0.11
Functioning tumors	1.12	0.53–2.35	0.75
Ki67[a] (%)	1.02	1.00–1.03	0.03
PC since NEN diagnosis	0.64	0.32–1.32	0.23
Other metastases at PC diagnosis	1.91	0.73–4.98	0.18
Size of peritoneal implants[a] (mm)	1.10	1.03–1.18	<0.01
Diffuse PC	3.05	1.25–7.45	0.01
Treatments before PC diagnosis	1.80	0.86–3.77	0.12
Number of previous surgeries	0.74	0.37–1.49	0.41
Multivariate analysis			
Ki67[a] (%)	1.01	0.98–1.05	0.45
Size of peritoneal implants[a] (mm)	1.10	1.02–1.20	0.01
Diffuse PC	4.75	0.55–40.91	0.16

PC, peritoneal carcinomatosis; HR, hazard ratio; CI, confidence interval; NEN, neuroendocrine neoplasm. [a] Continuous variable.

Peritoneal Disease Control

A total of 129 patients received a median of 2 treatments after PC diagnosis (range: 1–4). In detail, 43 patients underwent peritonectomy: 30 partial, 10 complete, in 3 cases associated with hyperthermic intraperitoneal chemotherapy (HIPEC). Ninety patients received SSAs, 32 PRRT, 50 CHT, 18 everolimus, and 1 sunitinib. Seventeen patients receiving CHT had a G3 neoplasm. Six cases received no systemic treatments after PC diagnosis due to poor conditions.

Overall, peritoneal DP occurred in 68 (50.4%) cases. Median PFS at peritoneal level was 72 months, with a 1- and 5-year survival rate of 80.5 and 52.6%, respectively (Fig. 1). Peritoneal PFS was accordingly influenced by the WHO 2017 classification [14] and PC diffusion, as represented in Figure 2 and Table 4 ($p < 0.01$).

Focusing on first-line therapy adopted after PC diagnosis, a statistically significant different peritoneal PFS ($p < 0.01$) was observed among the adopted treatments (Fig. 3; Table 4), with a poorer peritoneal disease control by PRRT (Table 5).

Considering all therapy lines, 12 out of 32 (37.5%) patients ever receiving PRRT had a peritoneal DP after the treatment. Nine (28.1%), affected by diffuse PC, had post-treatment clinical complications (bowel obstruction or

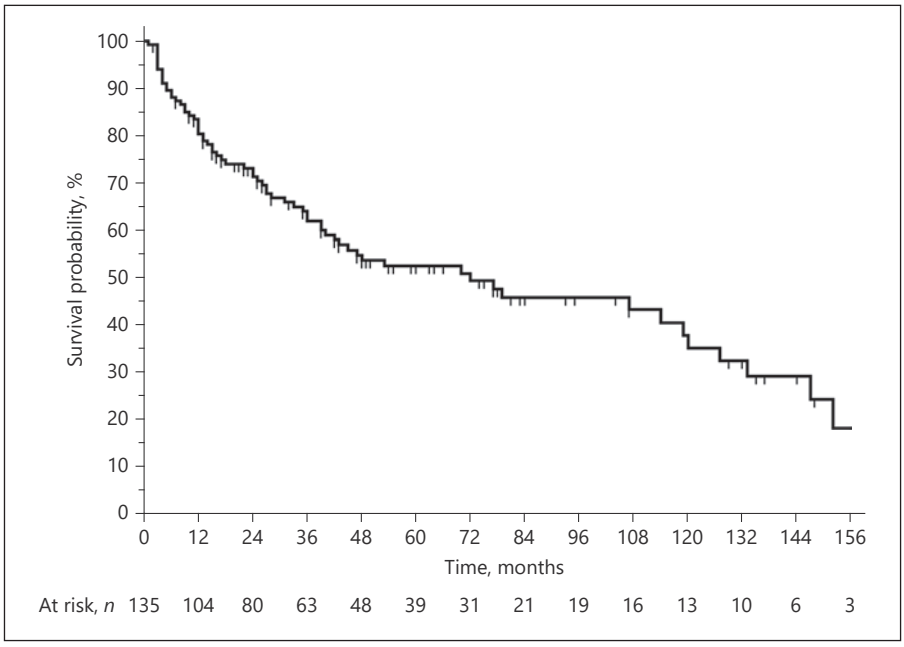

Fig. 1. Peritoneal progression-free survival (overall population).

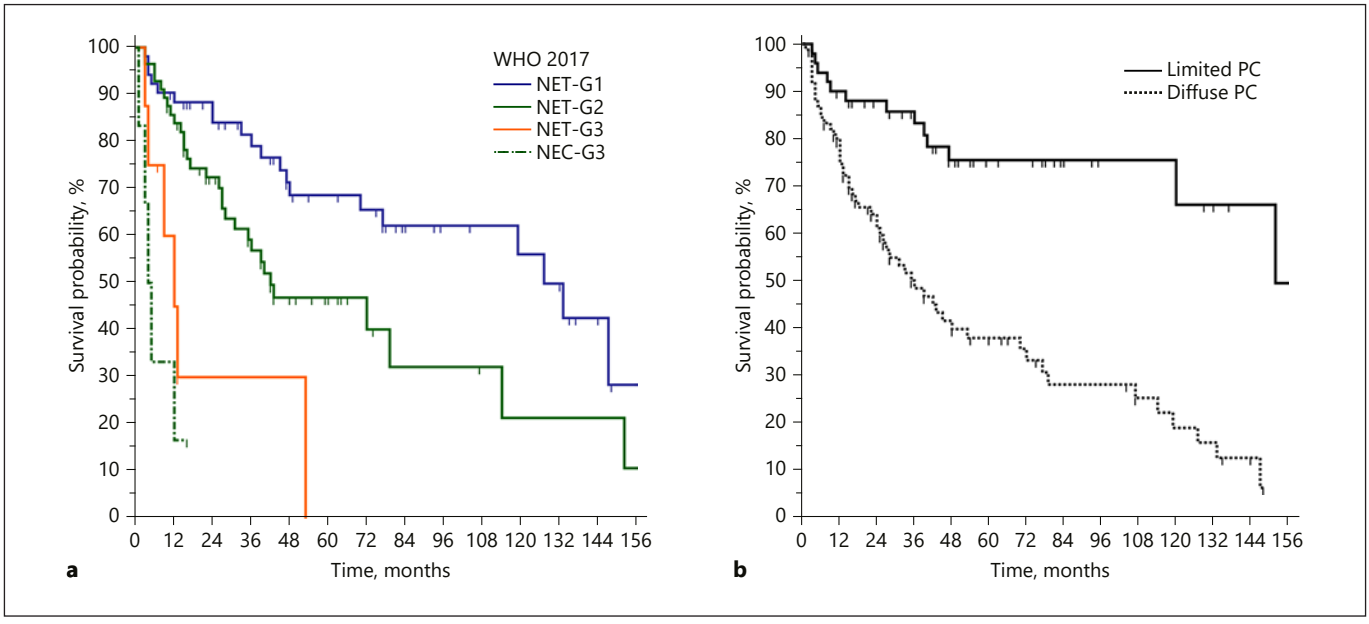

Fig. 2. Peritoneal progression-free survival according to cell morphology (**a**) and PC diffusion (**b**). PC, peritoneal carcinomatosis; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma.

ascites). One patient affected by diffuse PC with ascites, kidney dysfunction, and bowel obstruction died 4 months after starting PRRT treatment (Table 2).

With regard to peritoneal surgery, 7 cases (16.3%) had a G3 neoplasm and 4 of them (57.1%) had a peritoneal recurrence. Considering all 43 cases, no statistically significant difference was observed in terms of peritoneal RFS comparing patients facing only a partial resection, a complete peritonectomy, or the association with HIPEC (p = 0.45). Peritoneal recurrence in these subsets of patients was observed in 12/30 (40.0%), 3/10 (30.0%) and 2/3 (66.7%), respectively.

Table 4. Peritoneal progression-free survival analysis according to WHO 2017 classification, PC diffusion, and first-line therapy

Variables	Events, *n* (%)	PFS rates			*p*
		median, months	12-month, %	24-month, %	
WHO classification					
NET-G1	20 (38.5)	127	88.4	84.0	<0.01
NET-G2	30 (53.6)	42	83.9	72.3	
NET-G3	5 (75.0)	12	45.0	30.0	
NEC-G3	6 (83.3)	4	16.7	–	
PC diffusion					
Limited PC	13 (26.0)	152	90.0	74.7	<0.01
Diffuse PC	55 (64.7)	36	88.0	61.1	
First-line therapy					
Peritonectomy (partial or complete)	15 (36.6)	152	87.4	78.7	<0.01
Somatostatin analogs	26 (47.3)	114	89.1	79.5	
PRRT	7 (87.5)	25	62.5	50.0	
Chemotherapy	13 (65.0)	14	55.0	50.0	
Everolimus	4 (80.0)	35	80.0	53.3	

WHO classification according to WHO 2017 [14]. WHO, World Health Organization; PFS, progression-free survival; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; PC, peritoneal carcinomatosis; PRRT, peptide receptor radionuclide therapy.

Table 5. Risk of peritoneal disease progression according to first-line therapy

First-line therapy	HR	95% CI	*p*
Peritonectomy (partial or complete)	0.60	0.34–1.07	0.09
Somatostatin analogs	0.70	0.43–1.15	0.17
PRRT	2.67	1.21–5.89	0.01
Chemotherapy	1.83	0.99–3.35	0.05
Everolimus	1.98	0.72–5.44	0.19

HR, hazard ratio; CI, confidence interval; PRRT, peptide receptor radionuclide therapy.

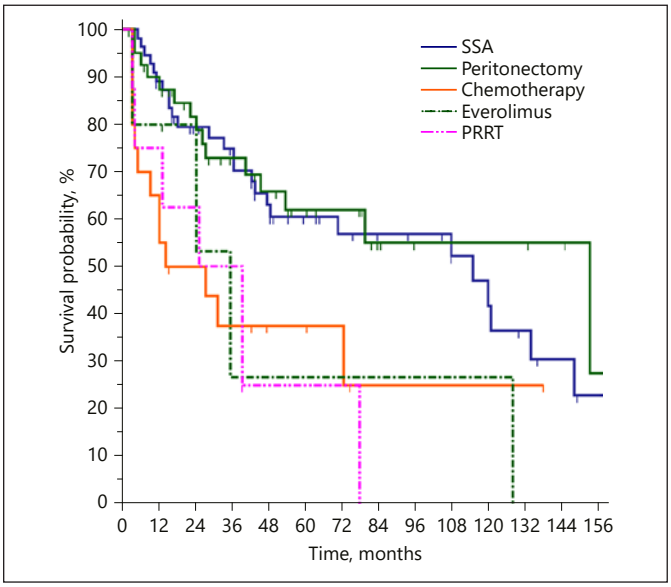

Fig. 3. Peritoneal progression-free survival at peritoneal level according to first-line therapy. SSA, somatostatin analog; PRRT, peptide receptor radionuclide therapy.

Discussion

This study shows how PC can represent a burden for GEP-NEN patients, causing clinical complications in about one fifth of them, with subsequent poor quality of life and often a need of extensive hospital admission irrespective of treatments. Amongst the available therapeutic options, PRRT showed relevant limits in patients with diffuse PC, due to the occurrence in about 30% of subjects of post-treatment clinical complications.

This series reports the longest follow-up for GEP-NEN patients after the diagnosis of PC (median 53.5 months). Its rationale was led by clinical practice, as in a significant proportion of patients PC is not an accidental finding but can seriously affect the clinical course, causing a broad spectrum of symptoms [3]. Our

data show size of peritoneal implants as the main risk factor for bowel obstruction (HR: 1.10, 95% CI: 1.02–1.20; $p = 0.01$). This result suggests a higher probability of this complication in the case of macroscopically visible nodules than for only microscopical peritoneal infiltration.

With regard to the control of tumor growth, our data showed a long-term stable disease at peritoneal level in the overall population (72 months), significantly influenced by histopathological features and PC diffusion. These results support the distinction between well-differentiated and poorly-differentiated NEN-G3 cases, which the novel WHO 2017 classification established for pancreatic patients [14], and also as a significant prognostic factor for non-pancreatic cases, and suggest its potential role in identifying patients at higher risk of peritoneal DP.

The present study also investigates the effectiveness of currently available treatments in controlling peritoneal disease in patients affected by GEP-NENs. A better peritoneal PFS was observed for patients treated at first line with SSA than with other systemic therapies (including PRRT, everolimus, and CHT). However, this observation might be related to a more favorable prognosis of the candidate patient to this treatment, characterized by a lower Ki67 and a more limited disease.

Only 43 (31.8%) patients in our series faced peritoneal surgery. Approaches were different (partial resection, complete peritonectomy, possible association with HIPEC) and no statistically significant difference in peritoneal RFS was observed with these options. The conclusion did not change even when performing the analysis excluding the cases with partial peritonectomy for focal infiltration ($p = 0.76$). This data might be related to the small number and heterogeneous distribution of cases in the three subgroups, but is also in agreement with the literature where the gold standard treatment for PC and the role of HIPEC in GEP-NENs are still under definition [10]. However, a higher rate of peritoneal recurrence was observed in cases receiving HIPEC. This result might be explained by a possible selection of patients with a more aggressive disease (diffusion of the PC or higher Ki67) as candidates for this approach in comparison to patients with a more focalized PC and suitable for a partial resection.

In nearly 40% of cases PRRT failed in controlling peritoneal disease (Table 2). Furthermore, about one fifth of patients receiving this therapy and affected by diffuse PC experienced bowel obstruction and/or ascites. In particular, in one case death occurred 4 months after treatment start (Table 2). These complications may be explained as radiation-induced peritonitis or paralytic ileus. Similar phenomena have been described in the literature for other neoplasms, such as ovarian carcinomas treated with external irradiation, and may be prevented by premedication with low-dose steroid starting on the day of PRRT and continuing 2–4 weeks after the therapy.

The correlation between PRRT and PC-related clinical complications as well as ineffective peritoneal disease control may suggest that this therapy should not be the treatment of choice in GEP-NENs with diffuse PC.

Conclusion

PC-related clinical complications are not uncommon events in GEP-NENs, especially in the case of large carcinomatosis nodules. PRRT should be prescribed with caution in patients affected by GEP-NENs and diffuse PC, due to the risk of poor disease control at peritoneal level and clinical complications. Larger series are needed to confirm these results.

Statement of Ethics

The authors have no ethical conflicts to disclose. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki, and was approved by the local ethics committee (EA1/124/19). Informed consent was obtained from the included patients.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

All authors conceived the study, designed the model, and gave the final approval of the manuscript. E.M. analyzed the data and wrote the manuscript with input from all authors. M.E.P. was responsible for overall direction and planning.

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