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RESEARCH

Gastric neuroendocrine neoplasms: analysis of a cohort of patients followed at the Brazilian National Cancer Institute

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Abstract

Objective: Gastric neuroendocrine neoplasms (G-NENs) are rare tumors categorized into subtypes, each exhibiting unique characteristics, levels of aggressiveness and prognostic implications. This study aimed to describe the experience on G-NEN management at the Brazilian National Cancer Institute.

Methods: Retrospective analysis involving all patients diagnosed with G-NEN from July 2000 to October 2022.

Results: 116 patients with G-NEN were identified; histopathological classification was possible in only 97 patients. Of these, 85 (87.6%) cases were of gastric neuroendocrine tumors (G-NETs) and 12 (12.4%) cases were of gastric neuroendocrine carcinoma (NEC). According to the WHO classification, 51 were classified as NET-G1, 31 as NET-G2, three as NET-G3 and 12 as NEC. Among the G-NETs, type 1 was most prevalent with 60 cases, followed by type 3 (eleven cases) and type 2 (five cases). Nonmetastatic patients were initially treated with endoscopic resection (59 patients), endoscopic surveillance (18 patients) and upfront surgical intervention (18 patients). For metastatic cases, treatment regimens included platinum-based chemotherapy, somatostatin analogs, peptide receptor radionuclide therapy and palliative surgical options. The median overall survival was 84.5 months for NET-G1, 73.4 months for NET-G2, 17.4 months for NET-G3 and 6.2 months for NEC.

Conclusion: This report presents the largest cohort of G-NEN in Brazil. While type 1 small G-NET generally exhibits indolent behavior, NEC is characterized by extreme aggressiveness. The survival outcomes observed in this treated population align with those reported in oncology centers from higher-income regions. This underscores the necessity for establishing reference centers dedicated to neuroendocrine tumors in low- to middle-income countries.

Keywords: neuroendocrine tumor; gastric neuroendocrine neoplasm; gastrin; therapy; survival

Introduction

Gastric neuroendocrine neoplasms (G-NENs) are rare, representing less than 1% of all gastric malignancies, and approximately 7% of all gastrointestinal (GI) tract neuroendocrine neoplasms (Nikou & Angelopoulos 2012, Gluckman & Metz 2019). The term G-NEN encompasses a heterogeneous group of neoplasm mostly derived from

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the enterochromaffin-like cells (ECL cells) of the gastric mucosa. Although an increase in incidence has been recently reported, most of this is due to small indolent well-differentiated tumors, diagnosed by the widespread use of upper gastrointestinal endoscopy (Sato *et al.* 2016).

G-NENs are classified as well-differentiated neuroendocrine tumors (G-NETs) – subdivided as low, intermediate or high grade based on Ki-67 proliferative index and neuroendocrine carcinomas (NECs), which harbors dismal prognosis. A G-NET subtype classification, based on pathogenesis and hormonal-related behavior, is commonly used in addition to the World Health Organization (WHO) pathology classification, as different subtypes show distinct clinical characteristics, pathophysiology, aggressiveness and prognosis (Burkitt & Pritchard 2006, Dias *et al.* 2017) (Table 1).

Type 1 is the most common and accounts for 70–80% of all G-NETs. It is characterized by high serum gastrin, clinically asymptomatic, usually presents as small and multiple lesions (≤10 mm) in the gastric body or fundus that rarely metastasize due to its nonaggressive behavior and good prognosis. Type 1 is often characterized by slow tumor growth and low risk of metastasis (less than 1%) (Panzuto *et al.* 2023). They typically occur in the setting of atrophic gastritis, with anti-intrinsic factor or anti-parietal cell autoantibodies, leading to macrocytic anemia, and sometimes posterior cord syndrome (Díez *et al.* 2013, Sato *et al.* 2016, Dias *et al.* 2017, Rinzivillo *et al.* 2022). Type 2 occurs when hypergastrinemia is associated with gastrinomas, sometimes associated with Zollinger–Ellison syndrome (ZES) and multiple endocrine neoplasia type 1 (MEN-1). Gastrinomas are usually smaller than 20 mm, located in the duodenum or pancreas, and its ECL cell hyperplasia corresponds to 5% of all G-NETs (Jordan *et al.* 2004, Díez *et al.* 2013, Panzuto *et al.* 2023). Type 3 G-NET develops sporadically, independent of gastrin secretion, with single lesions, generally greater than 10 mm, with more aggressive behavior and higher potential to generate metastases. Type 3 represents 15–25% of all G-NETs and has an unfavorable long-term survival (5-year survival rate 70%). Anemia, gastric outlet obstruction or weight loss may be present due to their larger size (Díez *et al.* 2013, Sato *et al.* 2016, Dias *et al.* 2017, Dillon 2020, Panzuto *et al.* 2023).

Ki-67 proliferation index is utilized to group the G-NETs into well-differentiated tumors, classified into G1 (Ki-67 <3%), G2 (Ki-67 (3–20%) and G3 (Ki-67 >20%), and poorly-differentiated tumors are defined as large- or small-cell neuroendocrine carcinomas with Ki-67 >20% (the majority having Ki-67 above 50%) (Ferrarotto *et al.* 2013, Sato *et al.* 2016). Endoscopic ultrasound (EUS) should be considered to evaluate lesions larger than 1 cm to determine depth of invasion and possible regional lymph node involvement. Depth of tumor invasion is related to worse prognosis and survival.

The ideal management of G-NET is still a matter of debate. Treatment of type 1 is centered on endoscopic removal of larger lesions, sampling and follow-up with endoscopic surveillance (Panzuto *et al.* 2023). However, patients with lesions larger than 10 mm or high Ki-67 labeling should be managed with snare polypectomy or endoscopic mucosal resection (EMR) (Exarchou *et al.* 2022*a*,*b*, Panzuto *et al.* 2023). Endoscopic full thickness resection (EFTR) with a lymph node sampling should be the treatment choice in patients with type 1 G-NET when EUS shows suspected lymph node metastasis or invasion of the muscularis propria. Antrectomy has been proposed, aiming to remove gastrin production by G cells. Some caveats of this unorthodox procedure are surgical complications and the possibility that some ECL cells have already acquired autonomy and no longer depend on gastrin stimulus for its growth (Dias *et al.* 2017, Vanoli *et al.* 2018, Exarchou *et al.* 2022*a*,*b*, Panzuto *et al.* 2023).

As G-NET type 2 can be associated with ZES and MEN-1, management involves localizing and treating the gastrinoma, which can be multiple. In these cases, if resection is not feasible, removal of the most prominent gastrinoma followed by surveillance is a viable option. For symptom management, somatostatin analogs should be considered (Norton 2005, Epelboym & Mazeh 2014). It is also important to screen the patients with MEN-1 for associated tumors on the pituitary and parathyroid glands. The sporadic gastrinoma are more often solitary, larger than 20 mm and located in the pancreas. When there is no evidence of metastatic

Table 1 Characteristics of gastric neuroendocrine tumors.

Characteristic	Type 1	Type 2	Type 3
Gastric pH	High	Low	Normal
Serum gastrin levels	Elevated	Elevated	Normal
Background	Chronic atrophic gastritis	MEN-1/ZES	Normal
Prevalence (%)	70–80%	5–10%	10–15%
Mucosa's histology	ECL hyperplasia, gastric body atrophy	ECL hyperplasia	Normal
Number of lesions	Multiple	Multiple	Single
Prognosis	Excellent. Low risk of metastasis	Uncertain	Poor. High risk of metastasis

MEN-1, multiple endocrine neoplasia type 1; ZES, Zollinger–Ellison syndrome.

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spread, surgical removal is indicated (Dias *et al.* 2017, Gluckman & Metz 2019). Before the development of an effective acid suppression therapy, the greater morbidity and mortality of ZES were related to complications of peptic ulcer disease, such as upper GI bleeding. The development of proton pump inhibitors resulted in a significant reduction in these events and prevented need for gastrectomy (Quatrini *et al.* 2005).

Type 3 G-NETs are candidates for radical resection, with total or subtotal gastrectomy and lymphadenectomy, due to the often advanced stage at the time of diagnosis and metastatic potential, especially with grade 3 tumor (Ki-67>20%) or diameter above 20 mm (Exarchou *et al.* 2022*a*,*b*). However, recent studies have demonstrated less invasive treatment options in type 3 G-NETs. Endoscopic mucosal resection appears to be more appropriate in those patients with tumor diameter less than or equal to 10 mm, classified as G1. It may also be an option in larger tumors, with a diameter smaller than 15 mm and Ki-67 <10%, when the risk of a surgical resection is high. In the remaining G1 patients, who do not meet these criteria, depth of invasion, tumor size and presence of lymph vascular invasion should be considered. EFTR could be safely indicated in these patients, measuring less than 20 mm, limited to the submucosa and without evidence of lymph vascular invasion (Min *et al.* 2018, Hirasawa *et al.* 2021, Panzuto *et al.* 2023). Less invasive treatment for type 3 G2 G-NET is still under debate. EFTR with lymph node sampling may be considered in those measuring between 10 and 20 mm after an individualized selection (Hirasawa *et al.* 2021). One study with 50 patients showed that type 3 G-NET smaller than 20 mm, invading up to submucosal layer, and no evidence of lymph vascular invasion could be successfully managed endoscopically (Kwon *et al.* 2013).

When surgical or endoscopic resection is not recommended due to several factors, such as advanced age, comorbidities, tumor location or disease recurrence requiring multiple endoscopic resections, the use of somatostatin analogs (SSA) is an option. It is associated with high response rate, 25–100%, but disease recurrence is frequent with therapy discontinuation (Strosberg & Kvols 2010, Rossi *et al.* 2020, Panzuto *et al.* 2023). Netazepide is a drug not available in Brazil that works through gastrin receptor inhibition and can be utilized in place of SSA. A complete response rate of 30% was observed on a phase II trial with 16 patients (Boyce *et al.* 2017). Similarly to SSA, drug discontinuation is associated with frequent relapses, so its clinical benefit should be better evaluated before recommendation for clinical practice.

In metastatic disease, treatment modalities should also be individualized and carried out through a multidisciplinary team approach. For patients with metastatic and potentially resectable disease, surgery should be considered, as it may improve control of symptoms and delay tumor growth. However, even with complete resection, most patients may experience disease recurrence (Riihimäki *et al.* 2016, Gluckman & Metz 2019).

A large proportion of patients with neuroendocrine tumors of the GI tract have liver metastasis. Therefore, in patients with unresectable and predominant hepatic disease, locoregional therapies should be considered, such as surgical cytoreduction, ablative therapy with embolization or radiofrequency ablation (Riihimäki *et al.* 2016, Machairas *et al.* 2021). Patients with disseminated and unresectable metastatic disease benefit from SSA as initial therapy for controlling symptoms and tumor growth. It is indicated for G-NET G1 or G2 with low Ki-67 (<10%) and high expression of somatostatin receptors in nuclear imaging. Patients with elevated Ki-67 may benefit from SSA in case of slow tumor growth or small disease volume (Strosberg & Kvols 2010). Peptide receptor radiation therapy (PRRT) using a radiolabeled somatostatin analog (lutetium 177) may be a treatment option. But there is still no consensus on the ideal timing for this therapy (Strosberg *et al.* 2021).

Everolimus can be utilized when previous therapies are contraindicated or after progression (Yao *et al.* 2016). Patients with progressive metastatic disease and NET G3 are suitable for cytotoxic chemotherapy with capecitabine, dacarbazine, fluorouracil, oxaliplatin and temozolomide. The mostly prescribed chemotherapy regimens use capecitabine combined with oxaliplatin or temozolomide (Ferrarotto *et al.* 2013, Strosberg *et al.* 2015). Most current clinical recommendations regarding G-NET care are based on retrospective studies due to the scarcity of prospective randomized trials – which are difficult to perform for G-NET.

This study aims to describe a cohort of patients with G-NET followed at the Brazilian National Cancer Institute (INCA) during the past decades. We sought to highlight differences in presentation, treatment and survival outcomes among the three subtypes. The study adheres to the strengthening the reporting of observational studies in epidemiology (STROBE) statement (https://www.strobe-statement.org/). INCA is part of the Brazilian public health system (SUS) and acts as the public cancer center of reference for all cancer types, including rare diseases. INCA also plays a role in formulating cancer-related recommendations and policies through the Brazilian Ministry of Health.

Materials and methods

Study design and setting

This is an observational retrospective study conducted by the Neuroendocrine Tumor Board (NTB). The NTB is comprised of providers from Medical Oncology, Endocrine Oncology, Abdominopelvic Surgical Oncology, Nuclear Medicine and Radiology

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departments of INCA. These providers collaboratively conduct multispecialty weekly meetings to discuss the NETs' case management.

Study population

Consecutive cases of G-NET were retrieved from an institutional database. Patients were considered eligible and included in the analysis if i) had histological diagnosis of G-NET and ii) had at least one medical appointment with treatment documentation at INCA between July 2000 and October 2022. Cases were excluded if had consultative encounters for second opinion at INCA and if they did not have a treatment plan documented at INCA.

Procedures

Clinical data review was based on hardcopy and electronic medical records from all patients included in the analysis. Data elements of interest included demographic information, disease presentation, characteristics, treatment-related data and follow-up information.

Pathological information regarding G-NET features (differentiation status, TNM staging, Ki-67 labeling index, local microscopic invasion degree and tumor clinical classification) was analyzed according to the original pathology report.

Ethical aspects

This study was approved by the INCA independent ethics committee in September 27th, 2020 (protocol 37278420.5.0000.5274) and conducted according to the principles expressed in the Declaration of Helsinki.

Statistical analysis

Analyses were performed using the SPSS version 20.0 for Macintosh (IBM, USA). Descriptive analyses were utilized to highlight the differences in presentation and treatment among the different G-NET subtypes. Categorical variables were expressed as percentages, while numerical variables were expressed as the mean ± standard deviation (SD) and/or median (minimum and maximum). The Kolmogorov–Smirnov test was used to evaluate whether numeric variables were normally distributed. The Kruskal–Wallis test was used to compare numerical variables among three or four independent groups and the Mann–Whitney test was performed for comparison between two groups. The means of normally distributed variables were compared using Student *t*-test. Chi-square or Fisher exact tests were used to evaluate categorical variables. A *P*-value <0.05 was considered statistically significant, except for comparisons among more than two groups, when *P*-values <0.017 (three groups) or <0.013 (four groups) were considered significant (Bonferroni post-hoc analysis). Survival outcomes among the three subtypes were analyzed with Kaplan–Meier survival curves. Data were analyzed up to May 15, 2024.

Results

Population characteristics

From July 2000 to October 2022, 116 patients with G-NEN were identified. No case of misdiagnosed G-NET was identified – Fig. 1. The median age at diagnosis was 55 years (17–87 years), with 66 (56.9%) female and 50 (43.1%) male. No significant difference was observed in terms of age between groups (Table 2).

A second malignancy was present in 22 patients and concomitant gastric adenocarcinoma was the most common, observed in five (4.3%) cases.

Regarding presentation at diagnosis, 40 (34.5%) patients had abdominal pain, 18 (15.5%) had anemia and 17 (14.7%) had weight loss as initial symptoms. Thirty-two (27.5%) were asymptomatic and had G-NETs incidentally diagnosed during an upper GI endoscopy routine examination (Table 2). Eight patients presented with upper GI bleeding (6.9%).

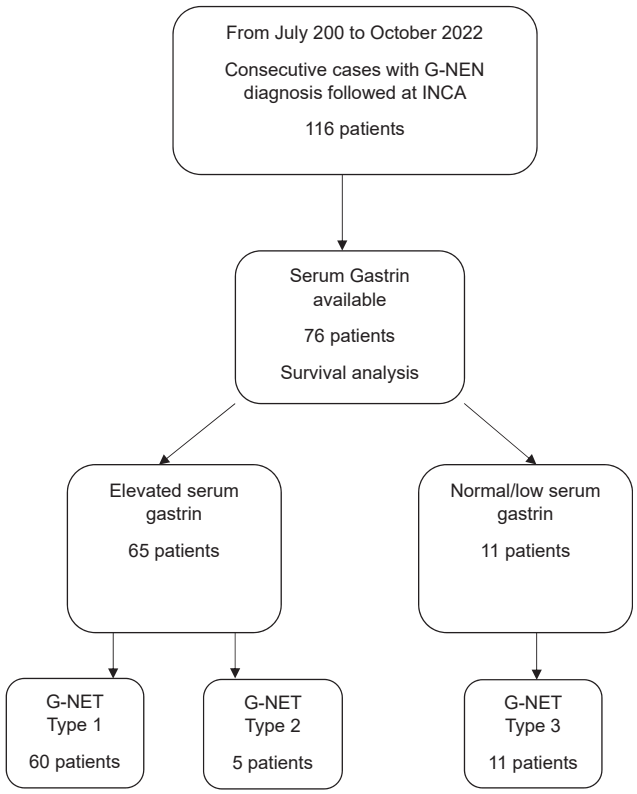

Figure 1

Study's included cases flowchart.

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Table 2 Population characteristics according to pathology classification.

	All patients (*n* = 116)	G1 (*n* = 51)	G2 (*n* = 31)	G3 (*n* = 4)	NEC (*n* = 11)	*P*
Age (years) (median)	55 (17–87)	56 (17–87)	49 (32–72)	66 (60–74)	69 (39–84)	
Gender	116	51	31	3	12	
Female	66 (56.9%)	33 (64.7%)	20 (64.5%)	1 (33.3%)	5 (41.7%)	0.290
Male	50 (43.1%)	18 (35.3%)	11 (35.5%)	2 (66.7%)	7 (58.3%)	
Tumor size (mm) (median)						
Endoscopy	6.0 (1–80)	5 (3–68)	6.0 (3–80)	31.5 (3–60)	40 (20–50)	
Pathology	7.5 (1–80)	7 (2–75)	9.5 (3–22)		65 (60–80)	
Tumor site	114	50	31	3	12	
Antrum	6 (5.3%)	3 (6%)	0	1 (33.33%)	2 (16.7%)	**0.001**
Cardia	6 (5.3%)	2 (4%)	0	1 (33.3%)	3 (25%)	
Body	74 (64.9%)	34 (68%)	22 (71%)	1 (33.3%)	5 (41.6%)	
Fundus	8 (7%)	2 (4%)	1 (3.2%)	0	2 (16.7%)	
Multifocal	20 (17.5%)	9 (18%)	8 (25.8%)	0	0	
Clinical classification (*n*)	76	42	20			
Type 1	60 (78.9%)	32 (76.2%)	16 (80%)	–	–	0.525
Type 2	5 (6.6%)	2 (4.8%)	2 (10%)	–	–	
Type 3	11 (14.5%)	8 (19%)	2 (10%)	–	–	
Initial symptoms (*n*)	116	51	31	3	12	
Abdominal pain	40 (34.5%)	18 (35.3%)	11 (35.5%)	1 (33.3%)	3 (25%)	**0.014**
Asymptomatic	32 (27.5%)	19 (37.2%)	8 (25.8%)	0	0	
Anemia	18 (15.5%)	8 (15.7%)	4 (12.9%)	1 (33.3%)	0	
Weight loss	17 (14.7%)	2 (3.9%)	6 (19.4%)	1 (33.3%)	7 (58.4%)	
GI bleeding	8 (6.9%)	4 (7.8%)	2 (6.5%)	0	1 (8.3%)	
GI obstruction	1 (0.9%)	0	0	0	1 (8.3%)	

GI, gastrointestinal. Bold indicates statistical significance.

In four of them, the bleeding was tumor-related and the G-NET width ranged from 20 to 75 mm; three of them had actinic endoscopic findings due to radiation therapy directed to a previously diagnosed malignancy (mainly gastric adenocarcinoma); one patient was diagnosed with esophageal varices due to chronic liver disease. Finally, one patient presented with initial GI obstruction (0.9%) due to a 65 mm pyloric G-NET. This patient was referred to an emergency surgery with subtotal gastrectomy and lymphadenectomy.

Presentation according to clinical classification was not different among the three groups, as described in Table 3.

Gastrin was measured in 76 patients (65.5%), of which 65 (85.5%) had levels above the normal range. Similarly, vitamin B12 was measured in 70 patients (60.3%), with levels below normal in 29 (41.4%). Therefore, G-NET clinical classification was possible in 76 patients (65.5%). Among the 76 cases properly classified by subtype, G-NET type 1 was the most frequent with 60 cases (78.9%), followed by G-NET type 3 with eleven cases (14.5%) and G-NET type 2 with only five cases (6.6%) – Fig. 1.

Table 3 Initial symptoms according to clinical classification.

Initial symptoms (*n*)	Type 1 60	Type 2 5	Type 3 11	*P*
Abdominal pain	20 (33.3%)	3 (60%)	7 (63.6%)	0.23
Asymptomatic	22 (36.7%)	1 (20%)	3 (27.3%)	
Anemia	15 (25%)	–	–	
Weight loss	2 (3.3%)	1 (20%)	–	
GI bleeding	1 (1.7%)	–	1 (9.1%)	
GI obstruction	–	–	–	

GI, gastrointestinal.

Tumor-related characteristics

Morphology

Primary gastric lesion location was available in 114 patients. Gastric body lesions represent 74 cases (64.9%), while lesions located at fundus, antrum and cardia corresponded to 7, 5.3 and 5.3%, respectively. Multifocality was observed in 20 patients (17.5%). The median tumor size according to upper GI endoscopy was 6 mm (range 1–80 mm). The median tumor size according to the pathological reports was similar to the findings of the upper GI reports (median 7.5 mm, range 1–80 mm). Mucosal restricted lesions were observed in 21 (28.4%) cases, whereas submucosal, muscularis and serosa invasion were described in 44 (59.5%), four (5.4%) and five (6.8%), respectively. The depth of tumor invasion was not assessed in 32 patients. Univariate analysis revealed significant association between tumor depth invasion and mortality (P = 0.034) (Table 4). Angiolymphatic invasion was present in 12 patients (20.7%).

Tumor grade

The Ki-67 index was evaluated with immunohistochemistry to define tumor grade as G1,

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Table 4 Tumor depth invasion and death.

	Death		
Depth of tumor invasion	**No**	**Yes**	**Total**
Mucosa	17 (81%)	4 (19%)	21 (100%)
Submucosa	37 (84.1%)	7 (15.9%)	44 (100%)
Muscularis	1 (25%)	3 (75%)	4 (100%)
Serosa	3 (60%)	2 (40%)	5 (100%)
Total	58 (78.4)	16 (21.6%)	74 (100%)

P = 0.034.

G2, G3 and NEC. Although the Ki-67 was not available in 21 patients (18.1%), two of them had NEC diagnosed in the histopathological report. Thus, tumor classification based on grade was defined in 97 patients as follows: 51 (52.6%) were classified as G1, 31 (32%) as G2, three (3.1%) as G3 and 12 (12.4%) as NEC. The median Ki-67 labeling index was 2% (0–2) for G1, 5% (3–15) for G2, 30% (30–60) for G3 and 80% (40–98) for NEC.

Tumor stage

At diagnosis, 98 (84.5%) patients (including multifocal duodenogastric gastrinomas) were diagnosed with locoregional disease, whereas distant metastasis was present in 18 patients (15.5%). Among the metastatic patients, two (11.1%) had NET-G1, two (11.1%) had NET-G3, six had (33.3%) NET-G2 and eight (44.5%) had NEC. Liver disease was present in all metastatic cases and was the only site of metastasis in nine (50%) of these. Four patients (22.2%) had peritoneal disease and two (11.1%) had bone metastasis in addition to the liver disease. One patient (5.6%) had bone, liver and peritoneal metastasis; one (5.6%) had lung, liver and cerebral metastasis; and one (5.6%) had duodenal, pancreatic and liver metastasis.

Therapy

Most patients 60.2% (59/116 patients) had endoscopic resections as initial treatment. Of these, 40 (67.8%) had regular endoscopic monitoring with successive resections and 19 (32.2%) underwent single resection. The endoscopic resections were performed on single lesions, or on the largest of multiple lesions, which were later followed every 6 or 12 months, as needed. Eighteen patients (18.4%) exclusively underwent upper GI endoscopic surveillance with regular examinations every 6 months or annually.

Eighteen patients (18.4%) had upfront surgery with curative intent: seven (38.9%) underwent subtotal gastrectomy with lymphadenectomy, five (27.8%) underwent total gastrectomy with lymphadenectomy, antrectomy was performed in two patients (11.1%) and one patient (5.6%) was treated with EFTR with lymph node sampling. Three patients (16.7%) clinically classified as type 2 G-NET were referred to surgical resection of the gastrinoma according to its location. Disease recurrence or progression occurred in five (27.8%) of these surgically treated patients: three had local relapse and two had distant metastasis (liver and bone).

Regarding the 18 metastatic cases at diagnosis, three cases (14.3%) lost to follow-up and one (4.8%) underwent exploratory laparotomy to evaluate curative resection, but was referred to palliative care due to the substantial peritoneal involvement, while four (19%) patients were referred to palliative care as initial treatment.

For the remaining metastatic patients, treatment involved conventional chemotherapy in four cases, somatostatin analogs (SSA) in three, PRRT in two and surgical resection in one case. Among the cases treated with chemotherapy, first-line protocols were carboplatin and etoposide (66.7%), capecitabine and oxaliplatin (16.7%), and capecitabine and dacarbazine (16.7%). Second-line therapy was performed in five cases, mostly a platin-based chemotherapy, except for one case treated with irinotecan. Topotecan was used in the only one patient exposed to third-line therapy.

Survival

The median follow-up for the entire cohort was 69.7 (0–243.8) months. Thirty-three (28.4%) patients died after a median survival of 18.8 (0.1–243) months. G-NET was the cause of death in 14 cases (42.4%). Among the 14 deceased, eight (57.1%) cases were classified as NEC, four (28.6%) as NET-G2 and two (14.3%) as NET-G3.

Death related to a second malignancy occurred in seven cases (21.2%) and from unknown cause in 12 patients (36.4%). The median overall survival according to the pathological classification were 84.5 months for G1, 73.4 months for G2, 17.4 months for G3 and 6.2 months for NEC (Fig. 2).

Discussion

To our knowledge, the present study reports the largest G-NET cohort to this date from a single Brazilian cancer center. Given the G-NEN rarity and the need of real-life reports from reference cancer centers (specially from low/middle-income countries), our study adds to the literature as we believe that the presented data might be of use due to the long follow-up observed. We believe that these data may serve as a benchmark for future policies and building of evidence in the field of this rare disease. Our findings highlight the importance of having providers from multiple specialties working collaboratively to define the appropriate approach to treat G-NET. Multiple specialties working together in the same institution is particularly important in the Brazilian public health system, where many patients would not have the ability to manage multiple referrals

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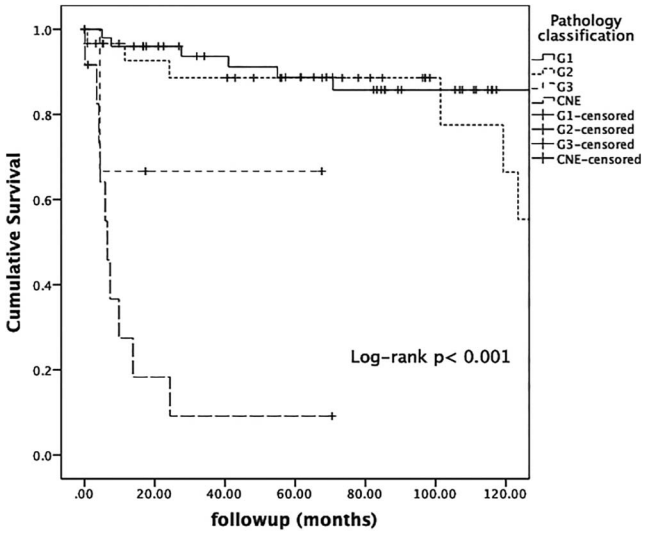

Figure 2

The median overall survival according to pathology classification.

and appointments at different facilities due to out-of-pocket expenses with food, transportation and procedures.

G-NET management relies on the pathological report of tumor differentiation, grade, extent of invasion and presence of poor prognostic features in addition to the subtype definition (Burkitt & Pritchard 2006, Sato *et al.* 2016, Dillon 2020, Exarchou *et al.* 2022*a*,*b*, Panzuto *et al.* 2023). Ideally, all these information should be available for patients with G-NET because they assist the healthcare team in defining the appropriate treatment and correlates with disease-specific survival (Ferrarotto *et al.* 2013, Sato *et al.* 2016). In our cohort, 34.5% of patients did not have subtype classification due to lack of serum gastrin evaluation, while 18.1% did not have Ki-67 index documented due to irregular public funding for specialized blood tests and immunohistochemistry. These challenges are often observed in limited resources settings, and lead to gaps in the availability of many tests and markers recommended as essential by international guidelines and treatment protocols. Our findings reinforce the need to create treatment protocols that take into account limited resources settings, such as many LMICs. Despite that, it is noteworthy that overall survival among our sample is similar to that described by cancer centers from high-income countries.

Among those patients with type 1 G-NET (8.3%) treated with surgical resection, one had high-risk criteria (endoscopy tumor size of 75 mm) and was treated with total gastrectomy and lymphadenectomy. The other three patients could have been treated with less invasive procedures as they had G1 G-NET smaller than 10 mm, confined to mucosa or submucosa. However, these disease characteristics were better defined after surgery with the surgical specimen evaluation. Interestingly, of the eleven patients classified as type 3 G-NET, the majority 63.6% (7/11) were treated with endoscopic resection. The tumors were confined to the submucosa, with sizes ranging from 5 to 10 mm; five patients had tumor grade G1 (with Ki-67 2%) and one had G2 (with Ki-67 5%). Three patients had more than one endoscopic resection and had stable disease at last follow-up visit, emphasizing the need for individualized patient evaluation and treatment planning.

Among the 14 patients (42.4%) who died due to the G-NET outcomes, nine patients had NEC, two had NET G3 and three had muscle layer invasion, reinforcing the importance of high risk features increasing the risk of death. Due to the prolonged follow-up, death due to unknown causes happened in 12 patients (36.4%). Seven patients (21.2%) died of second malignancy, highlighting the need for better practices of promotion of healthy habits and cancer screening among long-term survivors of cancer.

Our cohort results mirror many western studies outcomes. However, this study has limitations. Most of them are related to the study's retrospective nature. The lack of essential information limits the assessment of tumor classification and its relation to clinical main outcomes. In addition, it was not possible to evaluate the underlying gastric pathology due to the lack of investigation or report in the medical records, and gastrin was measured in 76 patients (65.5%), therefore, G-NET clinical classification was possible only in 76 patients (65.5%).

In conclusion, G-NEN is a rare neoplasm that includes different subtypes with different treatments and prognosis. This study highlights the need for individualized treatment planning and multispecialty collaboration for G-NEN management. These practices can help to tailor the treatment according to the tumors' behavior, utilizing less aggressive treatments when possible.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work reported.

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Author contribution statement

SC collected and interpreted data and wrote the manuscript. BPV performed data analysis and interpretation and manuscript review. CBC, RG and RR assisted with manuscript review. DB conceived the study, performed data collection, statistical analysis, assisted with interpretation of the results, wrote and edited the manuscript.

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