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Sporadic, non-functional, gastrin-producing duodenal neuroendocrine tumors: A retrospective study of an infrequent disease

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Objectives: Non-functioning gastrin-producing neuroendocrine neoplasms (NEN) of the duodenum are rare gastrointestinal tumors without a clinical syndrome due to gastrin production. Their incidence has significantly increased as an incidental finding during endoscopic studies. The aim of this study was to describe the characteristics and prognostic factors of this emergent and infrequent neoplasm.

Methods: We performed a retrospective observational study based on the duodenal NENs samples with positive staining for gastrin at the Department of Pathology, University Hospital 12-de-Octubre (Madrid, Spain) between 2000 and 2017. Patients with clinically functional tumors ([Zollinger–Ellison syndrome] or gastrin >1000 pg/mL), with previously diagnosed multiple endocrine neoplasia (MEN) syndrome or synchronous neoplasia were excluded. Clinicopathological and therapeutic variables, follow-up, recurrence, and mortality data were collected.

Results: In all, 21 patients were included. Most of the tumors were diagnosed incidentally as a single small polypoid lesion limited to mucosa/submucosa and with a low histological grade. Four (19.0%) patients presented with metastatic involvement at diagnosis (lymphatic and/or hepatic). These four patients also had a high or intermediate mitotic grade and infiltration further than submucosa. Local resection was applied in most cases as curative treatment. There were two cases of tumor recurrence and two tumor-related deaths with a 5-year disease-free survival of 81.0%.

Conclusions: The majority of these tumors were diagnosed at a localized stage and had a good prognosis with treatment. Nevertheless, given the potential metastatic risk, a close follow-up is necessary, especially in those with aggressive pathological factors such as deep infiltration or high histological grade.

KEYWORDS
duodenal neuroendocrine tumors, duodenum, neuroendocrine tumors, non functioning tumor, gastrin staining

1 | INTRODUCTION

Neuroendocrine neoplasms (NENs) are defined as epithelial neoplasms with morphological and immunohistochemical features of neuroendocrine differentiation.[1] Most gastrointestinal (GI) NENs are slow-growing neoplasms mainly located in the midgut, and their incidence has been significantly increasing during the last 40 years.[2,3] The cause of this increase is not yet definite, but it may be attributed to some extent to the availability of novel diagnostic techniques such as high-resolution imaging and an increased use of endoscopy.[4,5] Alcohol consumption and tobacco smoking are risk factors that have been linked to the emergence of NENs.[5]

NENs localized in the duodenum are rare, with an overall incidensce of 0.19/100 000 in the United States,[6] although recent studies suggest an increase in their incidence.[5] These tumors comprise 1%–3% of primary duodenal tumors, 11% of small intestinal NENs, and 5%–8% of all GI NENs.[3-7] Their overall annual incidence is reportedly low in the United Kingdom (0.04/100 000)[8] but high in Japan (0.64/100 000),[9] and they are slightly more common in males than in females.[10-12]

Duodenal NENs follow the most recent nomenclature for NENs by the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO) in 2018, based on a consensus conference held in November 2017.[13] This classification distinguishes between well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). NETs are also graded as G1, G2, and G3 on the basis of proliferative activity as assessed by mitotic rate and the Ki-67 proliferation index (G1 NET: mitotic rate <2/10 high-power field [HPF], Ki-67 index <3%; G2 NET: mitotic rate 2-20/10 HPF, Ki-67 index 3%–20%; G3 NET: mitotic rate >20/10 HPF, Ki-67 index >20%).[1] The morphological classification of NENs into NETs or NECs is supported by genetic evidence as well as by clinical, epidemiological, histological, and prognostic differences.[13] For example, absent *RB1* gene and aberrant *p53* expression may be useful to support a diagnosis of duodenal NEC, especially in the differential with G3 NETs. At the small gut, G1 NET (low-grade tumor) are the most frequent (50%–75%), followed by G2 NET (intermediate-grade tumor) (25%–50%). G3 NET (high-grade) and NECs are extremely rare (≤3%).[13,14]

An important clinical distinction among all NENs is their hormonal functionality.[12,14] Functioning NENs are defined as those associated with characteristic clinical syndromes related to an abnormal production of hormones by the neoplasm. Clinically non-functioning NENs may also produce hormones, which can be detected in serum or tumor cells using immunohistochemistry (IHC), but the hormones do not result in clinical symptoms.

Gastrin-producing NENs are the most frequent tumors and can be distinguished between functioning and non-functioning, conforming to the later definition.[12] Functioning gastrin-producing NENs, also called gastrinomas, may lead to Zollinger–Ellison syndrome. This syndrome was first described by Zollinger and Ellison, both of whom were surgeons at the Ohio State University, in 1955 and it is characterized by excessive gastrin secretion (defined as fasting serum gastrin >1000 pg/mL).[15,16] Its main features include recurrent peptic ulcer, gastroesophageal reflux, and occasional diarrhea. Symptoms related to this syndrome are present in 10% of the patients with duodenal NENs.[14,16]

On the other hand, non-functioning gastrin-producing NENs are mainly detected in the duodenum (90%).[12,17] Although they can appear in any part of the duodenum, most of them are located in the first or second part, and 20% are localized in the periampullary region.[10,11,14] They are usually small and solitary tumors that are incidentally diagnosed in an endoscopic examination. In fact, the presence of multiple NENs should raise the suspicion of multiple endocrine neoplasia or MEN syndromes.[12,15,17] Most gastrin-producing non-functioning duodenal NENs are typically limited to the mucosa or submucosa.[18] Like other duodenal NENs, they have the appearance of submucosal tumors that are either "hemispherical" or "flatly elevated". As a consequence, endoscopic biopsy may not always include all tumor tissues, and endoscopic ultrasonography (EUS) is essential to confirm the tumor size and depth of tumor invasion.[19] Metastases to lymph nodes can occur in 40%–60% of cases and liver metastases in up to 10% of patients.[20,21] However, despite this advanced presentation at diagnosis, most patients have prolonged survival due to a low proliferative rate of the tumors. Patients with well-differentiated duodenal NETs and localized disease have a 5-year overall survival rate of 80%–85%.[3] However, in those with distant metastases the rate decreases to 35–60%.[14]

In this study we aimed to describe the clinical and pathological characteristics of non-functioning gastrin-producing duodenal NENs diagnosed in our center in order to improve the information regarding their clinical presentation and disease course.

2 | PATIENTS AND METHODS

We performed a retrospective review of all the GI histological samples (surgically or endoscopically removed) with a diagnosis of NENs and a positve gastrin staining in the IHC examination between January 2000 and December 2017 at the University Hospital 12 de Octubre in Madrid, Spain. We selected this time period to cover the follow-up time that could be used to analyze the 5-year disease-free survival (DFS) of the most recent cases. Of all the samples, only those localized at the duodenum were recruited. Cases with one or more of the following criteria of functionality were excluded: (a) symptoms and signs of Zollinger–Ellison syndrome, including recurrent peptic ulcer, gastroesophageal reflux, and occasional diarrhea; or (b) basal fasting serum gastrin >1000 pg/mL. Patients with serum gastrin levels between 100 and 1000 pg/mL who had symptoms suggesting of Zollinger–Ellison syndrome and/or positive secretin test were excluded as well. We also removed patients with a previous diagnosis of familial disorders associated with NENs (multiple endocrine neoplasia or MEN syndromes) and those with a synchronous cancer at another site in order to include only sporadic cases and reduce confusing prognostic factors (Figure 1). The study protocol was approved by the local Clinical Research Ethics Committee (no. 18/418). Written informed consent was waived due to the retrospective study design.

2.1 | Clinical, biochemical and follow-up variables

The following data of the aforementioned cases were extracted from the electronic patient registry: patient's sex, age at diagnosis, type of diagnosis (incidental or not), symptoms and signs, indications for endoscopic examination, macroscopic view of the lesion and its location in the duodenum (first, second, third, or fourth part), serum levels of gastrin, the presence or absence of metastasis at diagnosis and the metastatic site, and type of treatment (endoscopic mucosal resection [EMR], surgery and other treatment strategies such as radiochemotherapy). In addition, the duration of the follow-up was recorded and the incidence of relapse, global mortality, and NEN-related mortality were calculated.

2.2 | Histopathological examination

Lesions were classified by their morphological differentiation and grading using Ki-67 index and the mitotic index in accordance with the WHO classification of 2018.[12,13] Therefore, when necessary, the original histological samples were reviewed and analyzed by the Pathological Anatomy Service for reclassification of the samples dating prior to 2018. Additional immunochemical staining techniques (absent *RB1* gene and aberrant p53 expression) were performed to distinguish NEC from G3 NET. We also recorded size of the tumor, depth of tumor invasion (mucosa, submucosa, muscularis propria, subserosal adipose tissue), and the presence or absence of vascular invasion, ulceration, or necrosis.

2.3 | Statistical analysis

All the statistical analyses were performed by using the SPSS Statistics version 25.0 (IBM, Armonk, NY, USA). Normal distribution of the continuous variables was tested by using the Kolmogorov-Smirnov test. Continuous variables with normal distribution were expressed as mean ± standard deviation, and those with non-normal distribution were expressed as median and interquartile range (IQR), when appropriate. While categorical variables were expressed as numbers and percentages or frequencies. A descriptive statistical analysis was performed.

3 | RESULTS

Of the 87 patients with a GI NET with positive staining for gastrin, 23 were localized in the duodenum. Of these, only two were excluded from the cohort study due to a basal gastrin level of over 1000 pg/mL. There were no cases in the context of multiple endocrine neoplasia. Ten patients did not have gastrin level tested at diagnosis but were included as non-functioning because they did not have any symptoms or signs of Zollinger–Ellison syndrome during the follow-up period. Altogether 21 patients with sporadic, non-functioning gastrin-producing duodenal NEN were included for analysis. All of them were classified as well-differentiated NETs. Additional immunochemical staining techniques (absent *RB1* gene and aberrant *p53* expression) were performed to distinguish the only case of G3 NET from NEC. Their clinical characteristics are summarized in Table 1.

3.1 | Presentations at diagnosis

Diagnosis was made as an incidental finding in the majority of patients (81.0%), usually during upper GI endoscopy performed for other indications, with dyspepsia being the most frequent complaint, followed by upper GI bleeding and iron deficiency anemia. In these cases, other findings explained the patient's symptomatology and the duodenal NEN did not justify the symptoms. Moreover, in two patients the diagnosis was reached through the study of metastasis of unknown origin, including a space-occupying lesion of the liver in one case and

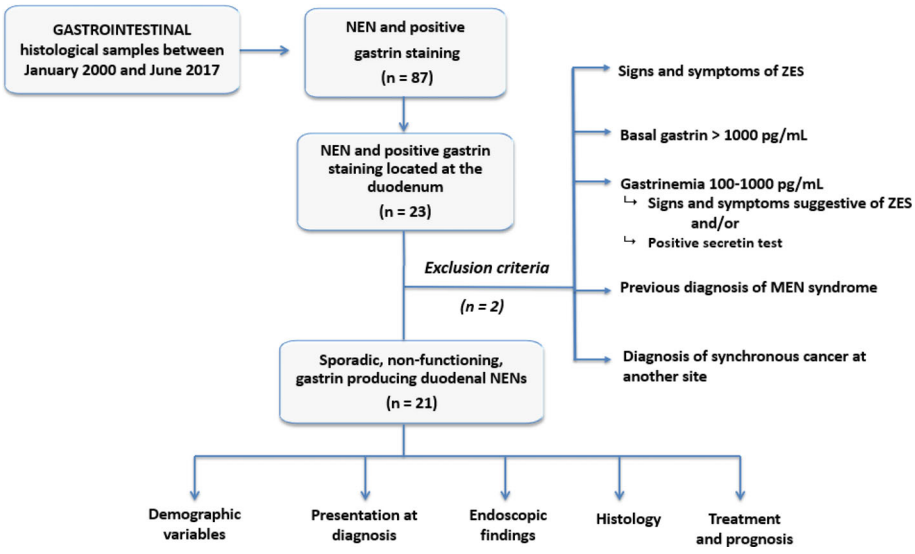

FIGURE 1 Study design and patient enrollment. Abbreviations: MEN, multiple endocrine neoplasia; NEN, neuroendocrine neoplasm; ZES, Zollinger–Ellison syndrome

TABLE 1 Clinical characteristics of the patients

Characteristics	Patients (n = 21)
Demographic variables	
Age, years (mean ± SD)	66.24 ± 11.51
Male sex (n, %)	13 (61.9)
Presentations at diagnosis	
Incidental diagnosis (n, %)	17 (81.0)
Serum gastrin, pg/mL (median [IQR])	165.0 (71.2–570.5)
Metastasis (n, %)	4 (19.0)
Lymphatic metastasis	2 (9.5)
Hepatic metastasis	1 (4.8)
Both	1 (4.8)
Indication for endoscopy (n, %)	
Dyspepsia	6 (28.6)
Iron deficiency anemia	3 (14.3)
Upper gastrointestinal bleeding	6 (28.6)
Abdominal pain	1 (4.8)
Constitutional symptoms	1 (4.8)
Recurrent vomiting	1 (4.8)
Lower gastrointestinal bleeding	1 (4.8)
Other	2 (9.5)
Endoscopic findings (n, %)	
Isolated polyp	11 (52.4)
Duodenal erosion or ulcer	5 (23.8)
Micronodules (resembling Brunner's gland hyperplasia)	3 (14.3)
Others	2 (9.5)
Location in duodenum (n, %)	
1st part (bulb)	16 (76.2)
2nd part	4 (19.0)
3rd part	1 (4.8)
Histology	
Size, mm (median [IQR])	8.5 (4.3–16.3)
Depth of tumor invasion (n, %)	
Mucosa	6 (28.6)
Submucosa	10 (47.6)
Muscularis propria	3 (14.3)
Whole intestinal wall	2 (9.5)
Grade (n, %)	
G1 (low)	11 (52.4)
G2 (intermediate)	5 (23.8)
G3 (high)	1 (4.8)
Not specified	4 (19.0)
Ki-67 index (n, %)	
<10%	15 (71.4)
10–20%	1 (4.8)
>20%	1 (4.8)
Not measured	4 (19.0)
Vascular invasion (n, %)	1 (4.8)
Necrosis (n, %)	1 (4.8)
Treatment (n, %)	
Endoscopic resection	8 (38.1)
Surgery	8 (38.1)
Chemotherapy (for disseminated disease)	4 (19.0)
None	5 (23.8)
Patient prognosis (n, %)	
Tumor recurrence	2 (9.5)
Duodenal	1 (4.8)
Hepatic	1 (4.8)
Follow-up, months (median [IQR])	25 (13–52)
Global mortality (n, %)	6 (28.6)
NENs-related mortality (n, %)	2 (9.5)

Abbreviation: IQR, interquartile range; NEN, neuroendocrine neoplasm; SD, standard deviation.

a lymphadenopathy in the other, both of whom had a gastrin-positive NET according to the histological study. Although most patients had a localized duodenal tumor, four of them were diagnosed at a metastatic stage, either with lymph node involvement (2/4 [50.0%]), hepatic involvement (1/4 [25.0%]), or both (1/4 [25.0%]).

Overall, the median serum level of gastrin was low (165 pg/mL) but it was only determined in 12 (57.1%) out of the 21 patients.

3.2 | Endoscopic findings

The most common site of these neoplasms was the first part of the duodenum (76.2%). Approximately half the tumors presented as an isolated polyp (Figure 2), while duodenal erosion or ulcer was the second most frequent endoscopic findings. Three of our 21 patients had micronodules resembling Brunner's gland hyperplasia in the macroscopic view but with a confirmed diagnosis of NET in the microscopic examination.

3.3 | Histology

In our cohort, non-functioning gastrin-producing duodenal NENs were characterized by their small size (median size 8.5 mm). In 16 (76.2%) of the 21 cases they did not extend further than the submucosa (Figure 3). Nevertheless, five cases had only a biopsy sample without EUS or EMR, so real profundity was not available. Two patients had the whole intestinal wall affected, presenting distant metastasis at diagnosis. Overall, histologic grade was low or intermediate (G1: 52.4%; G2: 23.8%) (Figure 4). Only one patient presented a high histological grade (G3) and had vascular invasion and necrosis. In this case, additional immunochemical staining techniques (absent *RB1* gene and aberrant *p53* expression) were used to distinguish G3 NET from NEC. Histologic grade could not be measured in 4 (19.0%) out of the

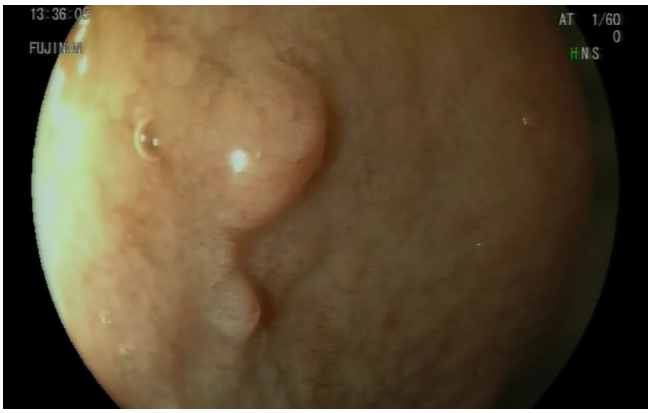

FIGURE 2 Endoscopic finding of non-functioning gastrin-producing duodenal neuroendocrine tumor

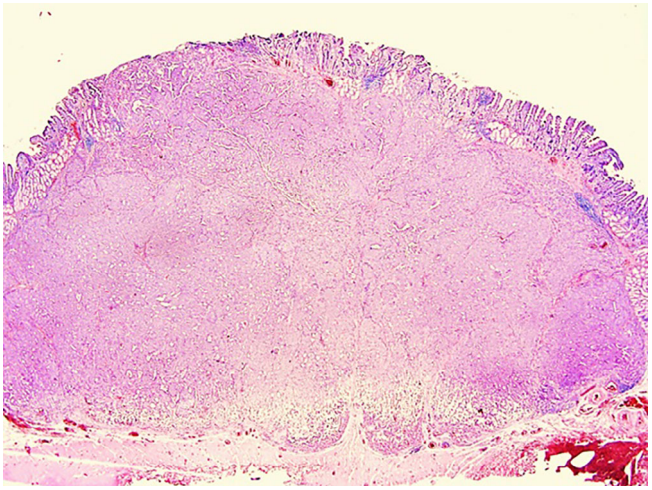

FIGURE 3 Submucosally resected non-functioning gastrin-producing duodenal neuroendocrine tumor. HE stain, ×12.5

21 patients due to an insufficient duodenal sample (n = 1) or failure to recover paraffin-embedded tissue to perform IHC staining (n = 3).

3.4 | Treatment

EMR was performed in 8 (38.1%) of the 21 patients and surgical intervention (duodenotomy or Billroth I and II gastrectomy) was also performed in 8 cases. Four (19.0%) patients received chemotherapy because of their disseminated disease. Remarkably, almost a quarter of the patients (5/21 [23.8%]) received no therapy at all, even though it was indicated. Of these five patients, three of them had no follow-up after endoscopic examination, with no specific review of the tumor; and the other two patients did not receive any treatment, arguing the benignity and low invasion of the tumor due to a superficial and low-grade duodenal NET without metastatic extension.

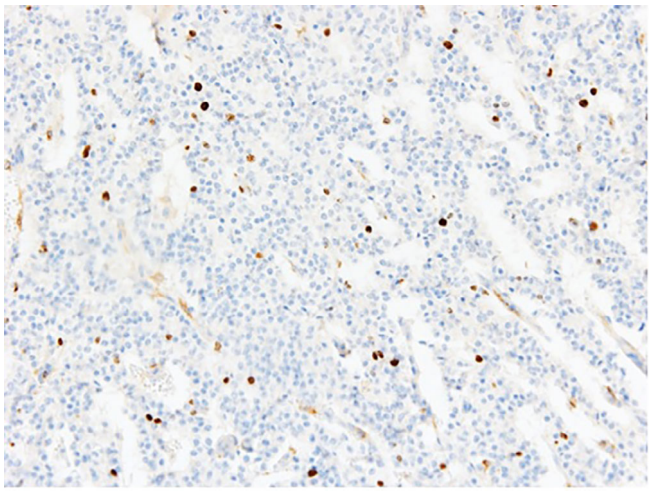

FIGURE 4 Ki-67 proliferative index (5%) of a case of non-functioning gastrin-producing G2 duodenal neuroendocrine tumor according to the World Health Organization classification (2018). Immunohistochemical staining, ×200

3.5 | Prognosis

The median follow-up period in our cohort was 25 months, with a disparate follow-up range among patients (IQR 13–52 mo).

Six of the 21 patients died during the follow-up period, but only two deaths were attributable to NEN, including one died 2 years after the diagnosis due to hepatic failure caused by progression of liver metastasis that the patient had since the diagnosis, and the other who died 4 months after the diagnosis caused by surgical complications following pancreaticoduodenectomy (intestinal obstruction by adhesions). This patient also had liver metastasis diagnosed incidentally during the abdominal computed tomography (CT) scan. In these two patients the tumor had vascular invasion, central ulceration and/or whole intestinal wall involvement, and an intermediate or high histological grade. Measurement of gastrin level was not performed in these two patients when liver metastases were diagnosed, but the tumors were considered clinically non-functioning as there was an absence of any systemic symptoms or signs of gastrin production. The other four deaths were due to unrelated causes, including neoplasms at other anatomical sites (head and neck, prostate, and esophagus) and heart failure; two of them died more than 5 years after the NEN diagnosis.

In all, in our cohort the 5-year overall survival rate was 81.0% and the median overall survival was 44 months (IQR 73.25 mo). Patients with tumors that were superficial (limited to mucosa or submucosa), with small size (<2 cm), and low grade (G1) presented a more favorable evolution after treatment, with a 5-year overall survival rate in this group of 88.9%.

There were hardly any relapses during the median follow-up period, with only two reported cases (recurrence rate 9.5%). The first case was a hepatic recurrence at the 4th month, which was an incidental finding in an abdominal CT scan performed due to small bowel obstruction that could not be treated because of the patient's death.

The other had a duodenal relapse at the 15th month after treatment that was successfully treated with a repeated EMR. In these two patients, the duodenal tumor extended further than the submucosa (muscularis propria and whole intestinal wall) and had an intermediate grade. The patient with duodenal relapse was diagnosed during a gastroscopy, without new symptoms and with a minimum increase of gastrin levels, which was insufficient to classify the relapse as a functioning tumor (31 pg/mL at diagnosis to 150 pg/mL, which was <1000 pg/mL). The other patient did not have gastrin measurement when liver metastasis was diagnosed, but was considered clinically non-functioning due to the absence of any systemic sign or symptom of gastrin production (Zollinger–Ellison syndrome).

4 | DISCUSSION

NETs of the GI tract are a heterogeneous group of neoplasms with a different clinical course and prognosis.[13,20] The incidence of these tumors in the duodenum is rising,[2] but they are still infrequent. There have been important additions to the literature on duodenal NENs, largely on epidemiological and pathological aspects.[4,5,13] However, because of their low prevalence, creating large registers and clinical trials is difficult. Therefore, their natural history and optimal management is unclear and sometimes misunderstood.[5] In the current study, we reviewed a cohort of patients with sporadic non-functioning gastrin-producing duodenal NENs in an effort to define the demographic characteristics, prognostic factors, and natural history of these tumors and provide more information about this infrequent pathology and its behavior.

The diagnosis of these tumors in the last 5 years has tripled in our center, showing the increasing incidence aforementioned and it is attributed mainly to the development of endoscopy. We observed a clinical presentation pattern in this type of tumor in our cohort. They usually occur in middle-aged men (66.24 years) and are diagnosed incidentally (81.0%) because of unspecific symptomatology. They are commonly a single and small lesion (<1 cm) located at the first part of the duodenum, with a polypoid aspect and superficial invasion (confined to the submucosa).

The rate of metastatic disease at diagnosis in our cohort was 19.0%. Of these patients, lymphatic involvement occurred in 9.5%, hepatic involvement in 4.8%, and both liver and lymphatic involvements in 4.8%, respectively. The rate of lymphatic involvement at diagnosis in our study is similar to that reported by Weatherall et al,[5] and is superior to the cohort of Rosentraeger et al.[12] However, distant involvement (hepatic metastasis) had not been previously described in the series reviewed. The two patients with liver metastases did not have gastrin measurement but they were not clinically functioning due to the absence of any systemic symptoms or signs of gastrin production. The relevance of distinguishing between non-functioning gastrin-producing NENs and gastrinomas, due to the presence of clinical symptoms related to the production of gastrin, lies on the different clinical course and management of both diseases.[5,12] Therefore, it is important not only to use the measurement of gastrin, but also an active search for symptoms for their correct classification.

In all patients with metastatic disease (lymphatic and/or liver involvement) we observed vascular invasion, macroscopic or microscopic ulceration, deep infiltration (further than the submucosa or whole wall involvement), and/or a high or intermediate histological grade. In fact, in the two patients with liver involvement the duodenal tumor extended further than the submucosa (muscularis propria and the whole intestinal wall) and had an intermediate Ki-67 index (3% and 5%) despite their small size and no data of vascular invasion or ulceration. Actually, the only patient in our cohort with a high-grade tumor (G3) was the only one with hepatic involvement at diagnosis and the patient died due to the progression of liver metastasis. In this case, the additional immunochemical staining techniques (absent *RB1* gene and aberrant *p53* expression) to distinguish G3-NET from NEC were very relevant for a correct classification. These data of poor histopathological prognosis could be an indirect parameter of metastatic disease and should be taken into account in the evaluation and management of these patients.

Regarding treatment, most non-functioning gastrin-producing duodenal NENs can be treated with EMR, as in most cases they are confined to the mucosa or submucosa and are well-differentiated, with an indolent course.[2,5] In our cohort, 38.1% of the patients were treated with EMR. However, 23.8% did not receive any type of treatment, even though it was indicated. This may be because their treating physicians underestimated the risk of these tumors, as they were superficial and well-differentiated in the biopsy. However, it is always necessary to complete the resection of the tumor to evaluate its exact depth of invasion and other pathological risk parameters such as those mentioned above. Furthermore, in those patients with a simple biopsy or without a complete endoscopic resection, an echoendoscopic study with mucosectomia or excisional surgery should be done for a correct determination of deep infiltration.

In relation to follow-up, two (9.5%) patients had recurrent disease following resection. One patient recurred locally and the other had metastatic disease to the liver. Both of them showed invasion further than the submucosa (muscularis propria and the whole intestinal wall) and an intermediate histological grade. For this reason, we consider that a close follow-up of these patients is necessary, especially in those with poor histological prognostic factors (infiltration further than submucosa, G2 or G3, vascular invasion or necrosis), due to the higher risk of relapse and metastatic disease they seem to have. On the other hand, those with low grade (G1), small size (<2 cm), and limited to mucosa or submucosa seem to have a very good prognosis, so these anatomopathological factors could be "prognostic clues" in daily practice for a more accurate treatment (complete resection) and follow-up.

In addition, we observed a very different duration in the follow-up period among patients. It might be a reflection of the lack of homogeneous consensus on the optimal duration of this period and the need for a clinical or histopathological risk profile that helps select patients who need a long-term follow-up.[2,20]

This study had several limitations, including its retrospective design and small sample size. Nevertheless, this study did have the largest cohort of non-functioning gastrin-producing duodenal NENs in Spain and one of the largest registered in Europe, providing more information about this emerging disease, especially about its clinical presentation and prognosis in real practice.

There are still unresolved issues in relation to the adequate staging, management, and follow-up of this type of duodenal NENs.[3,4,12] In fact, there is no consensus on the clinical practice guidelines regarding certain prognosis factors such as tumor size, vascular invasion, or tumor depth.[20] Moreover, it is still difficult to establish a validated protocol to address the existence of synchronous tumors and the criteria of familiar screening. Therefore, more evidence about the natural course, clinical presentation, and prognosis factors of these neoplasms is necessary.

In conclusion, our findings on non-functioning gastrin-producing duodenal NENs are consistent with previous data and provide some clinical and histopathological risk factors with 5-year overall survival. Although these tumors have a more indolent course than gastrinomas, complete resection is necessary due to their potential risk of recurrence and distant metastasis regardless of their size, especially those with poor histological prognostic factors (infiltration further than submucosa, intermediate [G2] or high-grade [G3] tumor, with vascular invasion or necrosis). EMR is a minimally invasive and a successful curative treatment in low-risk tumors (limited to mucosa or submucosa, <2 cm in size, and low-grade [G1] tumor). However, periodic revision is mandatory to detect possible recurrence. The duration and prognosis factors to take into account during the follow-up remains unclear; therefore, more studies are warranted.

CONFLICT OF INTEREST

The authors had no conflicts of interest to declare.

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