Endoscopic management of gastric neuroendocrine tumors

Martín Gómez Zuleta, MD,[1] William Otero Regino, MD,[2] José Pion Otero, MD.[3]

[1] Professor of Gastroenterology at the Universidad Nacional de Colombia and Gastroenterologist at Hospital El Tunal and Endosono Ltda in Bogotá, Colombia.
[2] Professor of Gastroenterology at the Universidad Nacional de Colombia and Gastroenterologist at Hospital El Tunal and Fundadores Clinic in Bogotá, Colombia.
[3] Gastroenterologist at Hospital El Tunal in Bogotá, Colombia.

Translation from Spanish to English by T.A. Zuur and The Language Workshop

Received: 25-01-11
Accepted: 02-08-11

Abstract

Introduction: Nowhere in the world is there a clear guide for what we must do for patients with gastric neuroendocrine tumors (gastric NETs). Although mucosectomy is often advised for lesions of less than 1cm in which there are no metastases, some groups advocate surgical management. In addition, it is not clear how treated patients should be followed up. The aim of this study is to describe our experience in the endoscopic management of these patients.

Patients and methods: This is a retrospective and descriptive study conducted over a 4 year period at two institutions. Different variables were recorded in a data collection instrument specifically designed for this investigation. Data collected included socio-demographic characteristics, clinical presentation of symptoms, endoscopic findings, tests ordered, whether surgical or endoscopic treatment was chosen, descriptions of endoscopic technique used for resection, the number and sizes of lesions, patients' clinical development and patient outcomes.

Results: Altogether the study included 29 gastric NET patients who had a total of 43 lesions. 28 patients had were NET type I tumors while one case was type III. The average age at diagnosis was 55 ± 10 years; 64% were women. 23 patients had tumors in the gastric corpus, 4 in the gastric fundus and 2 in the antrum. 14 patients (17.2%) had pernicious anemia. All 28 patients with type I NETs were treated endoscopically. Endoscopic methods included 17 (60.7%) mucosectomies with loops, 4 (14.2%) mucosal resections with caps, and 7 (25%).mucosectomies with bands. Surveillance of patients from diagnosis to the date of the study averaged 32.5 months (6 - 47 months). The patient who had been diagnosed with NET III died. The survival rate for patients with type I gastric NETs is 100%.

Conclusion: Patients with Type I NETs have excellent prognoses. In this study their survival rate was 100% during the follow-up period. Endoscopic treatment is safe and effective for these patients when the mucosectomy techniques described in the literature are used.

Keywords

Neuroendocrine tumor, stomach, endoscopic mucosal resection, cancer.

Gastric neuroendocrine tumors (GNETs), although still very rare, are being found increasingly often. This is probably due to increased use of endoscopic examinations, the advent of imaging tests including endoscopic ultrasound, computed tomography (CAT scans) , magnetic resonance imaging (MRI), and positron emission tomography (PET scans); and to the introduction of immunohistochemistry (1). Because of its rarity, heterogeneity and complexity, GNETs continue to be diagnostically challenging and difficult to treat (2). NETs were described over 100 years ago by Lubarsh (3), and in 1907 the term "karcinoid" was introduced by Oberndorfer (4). However, it was not until 1923 that GNETs were first called gastric carcinoids by Askanazi (5). Although the term carcinoid has been very

popular, the WHO recommends that its use be discontinued because it creates confusion. Instead it has designated it as a neuroendocrine tumor (NET) since these tumors originate from neuroendocrine cell networks that are present in almost all organs (6,7).

GNETs originate from enterochromaffin-like cells (ECLs) of the gastric corpus that normally produce histamine which is involved in the regulation of gastric acid secretion (8,9). Neoplastic changes in these cells are often associated with elevated levels of serum gastrin (10). GNETs represent 8.7% of all neuroendocrine tumors of the gastrointestinal tract and less than 1% of all malignant tumors of the stomach (11). Between 0.6% and 3% of all resected gastric polyps are GNETs (12). In a study in Colombia of 150 patients with polyps, 5 patients were found to have GNETs (3.3%) (13).

Classically three types of GNETs have been described (14). Type I accounts for 70% to 80% of these tumors (15). These tumors are polypoid, are usually less than 1 cm in diameter, have a central depression or ulceration, are located in the corpus and gastric fundus and are associated with hypergastrinemia and atrophic gastritis (16). Less than 10% of Type I GNETs less than two inches in diameter metastasize (17). Type II is either associated with Zollinger-Ellinson syndrome or is develops as part of multiple endocrine neoplasia (MEN) Type I syndromes. Type II GNETs account for 5% of GNETs. They are accompanied by hypergastrinemia (18). Type III, sporadic GNETs, accounts for 15% to 25% of these tumors (17). They are usually single tumors with diameters over 2 cm that are not associated with hypergastrinemia. Type III tumors are very aggressive with great potential for metastasis. The five year survival rate of Type III patients is less than the 75% (19). Recently Type IV has been described, but it is more like an endocrine carcinoma than a GNET (20).

Gastric, lung, intestinal and other neuroendocrine tumors are classified into three groups based on pathology according the WHO (21).

1. Well-differentiated (so-called carcinoid) tumors are benign non-functioning tumors which are noninvasive and are confined to the mucosa and submucosa.
2. Well-differentiated neuroendocrine carcinomas (malignant carcinoids) are sporadic non-functioning tumors which exhibit low-grade malignancy, invade the muscles, metastasize and are more than 2 cm in diameter.
3. Poorly differentiated neuroendocrine carcinomas which exhibit a high grade of malignancy.

Parameters used to determine overall prognosis include tumor type, presence or absence of vascular invasion, mitotic index, Ki67 index (histologic proliferation marker) and tumor size (22). These lesions may be classified as having low potential for malignancy when the tumor size is less than 1 cm and there is vascular invasion, or as having high potential for malignancy when tumors have histological grade 2 or 3, a mitotic index greater than 9, Ki67 greater than 30%, or are larger than 3 cm. Lesions found between these two extremes fall into an intermediate category in which the best forecast can only be an estimate based on the type of tumor (22).

Internationally, no clear guidelines have yet been developed for what we should do for patients in whom we find a gastric NET. Although mucosectomy is often advised for lesions of less than 1cm which have not metastasized, some groups advocate the use of surgical management. In addition, it is not clear how treated patients should be followed. Unanswered questions include whether scintigraphic imaging with Octreoescan should be used and whether endoscopies should be performed every 3 months or every 12 months. The aims of this paper are to describe our experience in endoscopic management of these patients, to show how these lesions were evaluated and resected, and to show how these patients evolved over the past four years. Patients were treated at two institutions: Hospital El Tunal, a fourth-level state institution, and at Endosono Ltda. center where gastric endoscopies were performed.

MATERIALS AND METHODS

This is a retrospective descriptive study which was conducted for the period between December 2005 and December 2009 at two health institutions in Bogota, Colombia: Hospital El Tunal, a 4th level public hospital of referral, and Endosono Ltda. center , a private institution to which patients are referred for special gastrointestinal examinations. Using the databases of these two institutions, patients with gastric NETs were identified from gastric endoscopies performed at Hospital El Tunal and from gastric endoscopic ultrasound (EUS) images taken at Endosono Ltda. center. Different variables were recorded using a data collection instrument specifically designed for this investigation. It included socio-demographic characteristics, clinical presentation (associated symptoms), endoscopic findings, tests ordered, and treatments prescribed (surgery or endoscopy). It also recorded a description of the endoscopic technique used for resection, the number and size of lesions, and the patient's clinical evolution and outcome. All information was obtained by reviewing the medical records of all patients in the database of the Hospital El Department of gastroenterology and endoscopy who had been diagnosed with neuroendocrine tumors, resected gastric polyps and tumors characterized as "carcinoid". Patient characteristics identified in the Department of gastroenterology and endoscopy database were correlated

with the database of the hospital's pathology service. Only patients for whom complete information was available were included in this study. Information required included a definitive histological diagnosis of neuroendocrine tumor in which hematoxylin-eosin and PAS were complemented by immunohistochemical reaction with chromogranin A and cytokeratin AE1AE3. In some cases studies of specific neuronal enolase and synaptophysin were conducted. Diagnoses of pernicious anemia were based on multifocal atrophic gastritis and positive anti-parietal cell antibodies.

RESULTS

From the four years of the study at Hospital El Tunal, 1,450 colonoscopies and 10,718 endoscopies were reviewed. 44 patients were found with neuroendocrine tumors: 29 tumors were in the colon, and 15 were gastric NETs. The prevalence for all colonic tumors was of 3.4%, but the prevalence of GNETs was only 0.14%. There were no duodenal NETs. During the same period, 236 gastric neoplasms were found (an average of 58.2 per year). 218 of these were adenocarcinomas (2% of all endoscopies), 3 were gastrointestinal stromal tumors (GIST) and 15 were neuroendocrine tumors (3.8 per year). These represent 6% of all gastric tumors. At Endosono Ltda. center, 14 gastric NETs were identified from 2,130 gastric endoscopies resulting in a prevalence of 0.65%. In total, the study included 29 patients with NETs. These patients had a total of 43 lesions. 19 patients (65.5%) had only a single lesion each. One patient had 7 lesions.

The general characteristics of patients with gastric NETs are shown in Table 1.

Table 1. Patient characteristics.

Age (years)	55 years (10)
Range (years)	35-85 years
Sex f / m	19/10
Epigastric pain / dyspepsia	20 (65,5%)
Fatigue	2 (6,8%)
Anemia	8 (27%)
Diarrhea	1(3,4%)
Flushing	1 (3,4%)
GERD	1 (3,4%)
Did not cause symptoms	8 (27%)

Pathology. In all cases, diagnoses of neuroendocrine tumors were based on biopsies of gastric polypoid lesions and immunohistochemistry which identified chromogranin A. The superficial and deep edges of resection specimens from each patient who was referred for a mucosectomy were evaluated for lymphovascular invasion. The Ki-67 proliferation index was assessed in only 15 cases of the 28 Type I cases (53.6%). The result was less than 2% in all cases indicating good prognoses (11).

In our series, 28 tumors were NET Type I and one case was Type III. We found no type II cases.

Clinical features. The mean age at diagnosis was 55 ± 10 years with ages ranging from 35 to 82 years. 64% were women. Patients were referred for endoscopies for epigastric pain (19 cases), symptoms of gastroesophageal reflux disease (1 case), possible chronic anemia (8 cases including 2 cases of fatigue, 2 of pallor and 2 cases of weakness).

An 82 year old female patient had carcinoid syndrome with a Type III tumor which had metastasized to the liver. The patient died after 6 months of follow up.

Endoscopic findings showed 23 gastric corpus tumors, 4 tumors in gastric fundi, and 2 cases of isolated lesions in the antrum. 14 patients (17.2%) had pernicious anemia (Figure 1).

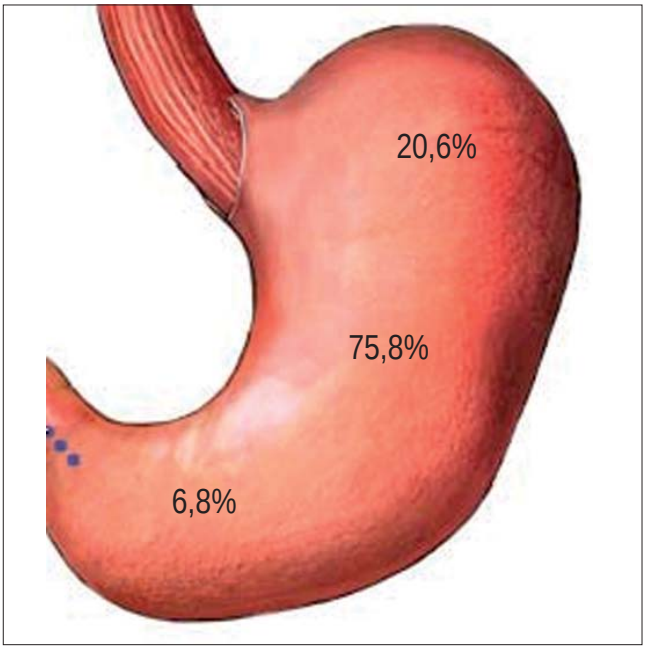

Figure 1. Distribution of NETs in the stomach.

Hypergastrinemia. All patients were checked for hypergastrinemia. Gastrin levels were elevated in all 28 Type I cases (Figure 2), but were normal in the one Type III case (Figure 3). The average gastrin level was 1,223 ± 313.74 pg/ml with a range between 615 and 1,500 pg/ml. Normal levels are below 200 pg/ml.

Endoscopic sonograms were taken of 18 patients (62%). They revealed seven hypoechoic lesions (39%) in the

lamina muscularis mucosae or second layer of the mucosa. The other eleven patients (61%) showed partially compromised submucosal membranes although there were no cases of perigastric lymphadenopathy and none of these lesions involved the muscularis propia or celiac artery. It is important to note that no endoscopic sonography was performed on the patient with Type III tumor.

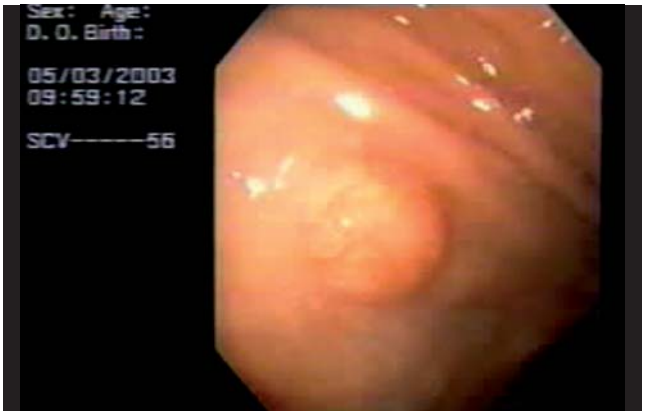

Figure 2. Patient with elevated lesion at the greater curve, note that it has a reticular pattern which is characteristic of NETs, in this case is a type I.

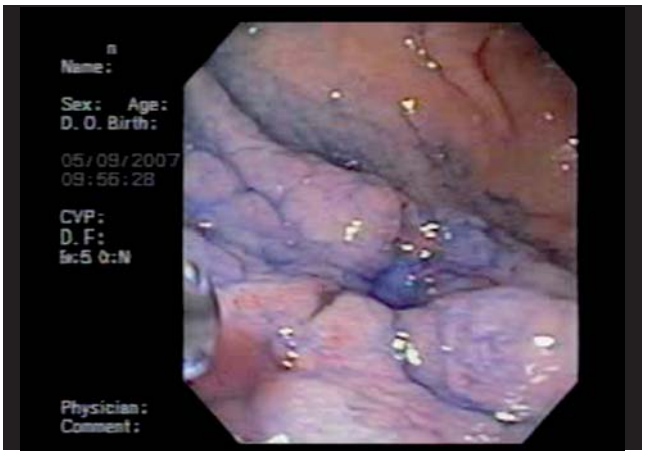

Figure 3. Patient with ulcerated lesion on greater curvature of the antrum, the pathology confirmed a type III TNE.

Treatment. In our series, endoscopic polypectomies were performed (Figure 4) with and without mucosectomies, on 27 patients. A partial gastrectomy (resection of the lesion plus antrectomy) was performed on one 36 year old patient who had seven Type I carcinoids. The patient was followed up with a series of endoscopic examinations. Although endoscopic resections were performed to remove these lesions, a mucosectomy had to be performed to remove the primary lesion which measured 20 mm in diameter and had positive edges. In this situation we was decided to perform a wedge resection of the lesion and an antrectomy to eliminate gastrin producing G cells. At the time of the endoscopic check up three months after the procedure, gastrin levels had normalized, and there were no residual or recurrent lesions.

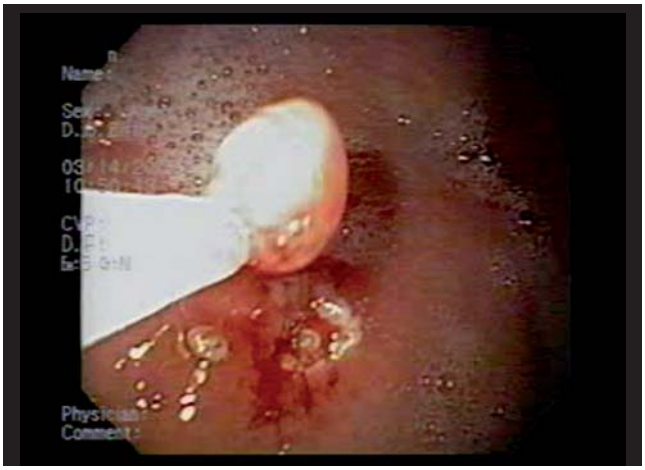

Figure 4. Patient with type I NET. Polypectomy carried out with loop, observe the polyp in the loop and the secondary ulcer.

In total, 28 patients with type I NETs had 42 tumors. 24 patients had 1 to 3 lesions and 4 patients had 4 to 7 lesions (Table 2).

Tabla 2. Endoscopic management features in NET.

Features	# patients	%
Endoscopic Tx	27/28	96,4%
Size 2-20 mm injury		
1-5 mm	20/42	47,6%
> 5-10 mm	10/42	23,8%
> 10-15 mm	8/42	19%
> 15 mm	4/42	9,5%
Number of lesions n = 42		
1-3 lesiones	24/28	85,7%
4-7 lesiones	4/28	4,3%
Mucosectomy with handle	17/28	60,7%
Mucosectomy with cap	4/28	14,2%
Mucosectomy with band	7/28	25%

Lesion diameters ranged from 2mm to 20 mm: 20 lesions were between 1mm and 5 mm (47.6%), 10 lesions were between 5mm and 10 mm (23.8%), 8 lesions were between 10mm and 15mm (19 %), and 4 lesions were larger than 15mm (9.5%).

All 28 patients with Type I NETs were treated endoscopically. 17 patients of these patients had mucosectomies with loops (60.7%), 4 had mucosal resections with caps (14.2%), and 7 had mucosectomies with bands (25%).

Only one case had edges compromised by the lesion. This patient underwent cap mucosectomy and an antrectomy.

In 24 patients we used a single session endoscopic resection of tumors and in 4 (14.3%) it took two sessions with an interval of 3 months to eradicate them. 3 cases (10.7%) showed recurrence of lesions in endoscopic control at 1 year and were also managed by endoscopic resection.

Once lesions were resected the patient was sent home. Patients were restricted to a liquid diet for the following day and prescribed 40 mg of omeprazole daily for 6 weeks with an endoscopic checkup after 3 months. We followed the same scheme we published in an earlier article for patients who underwent gastric mucosal resections for adenocarcinoma (23).

Only one of the resected lesions (in the case of the patient who underwent surgery) had compromised lesion edges. The other 41 had deep lateral edges which were free of lesions and which had no lymphovascular invasions.

Patients were monitored for an average of 32.5 months (6 to 47 months) from the moment of diagnosis to the date of the study. The one patient diagnosed with a Type III NET died. Since this was the only mortality, the rate of survival of patients with Type I gastric NETs is 100%.

DISCUSSION

In this study we found 29 gastric NETs: 15 at the Hospital El Tunal and 14 at Endosono Ltda. center. The prevalence rates at the Hospital El Tunal were 0.27% of all gastrointestinal endoscopies and 6% of all gastric malignant tumors at the institution. The prevalence rate at Endosono Ltda. center was 0.65% of all eco-gastric endoscopies. This is one of the largest reported series in which the endoscopic management was the primary method used for eradication of these lesions.

In other studies gastric NETs represent less than 1% of all malignant tumors of the stomach (11, 24). In contrast this study found a prevalence rate for gastric NETs six which was times higher. Although this cannot be easily explained, it should be noted that the department of gastroenterology and endoscopy of the Hospital El Tunal is referral unit for the city of Bogotá and some municipalities in Cundinamarca. Nevertheless, we cannot rule out errors in the pathological diagnosis such as those which have been reported in other studies (24). We believe that the prevalence of gastric neuroendocrine tumors may be higher in Colombia than in other countries and that it is increasing every day as has been suggested by a recent English work which showed a significant increase in gastric NETs in the last decade (25). As a result, our findings justify further studies here in Colombia. These studies should be multi-institutional in order to determine the true prevalence of this entity among all gastric tumors and gastric polypoid lesions. In other places the prevalence of NETs among gastric tumors and gastric polypoid lesions is considered to be 0.6% to 2% (11-13). The prevalence of these tumors at Endosono Ltda. center of 0.65% probably reflects the fact that it is a referral center which concentrates on already diagnosed tumors.

It is important to note that all of the patients who were referred for endoscopic sonograms to evaluate the size and depth of tumors had primary lesions larger than 10 mm. This is consistent with recommendations for using this examination for these lesions (11). Although we do not have data on the frequency of these tumors found in upper gastrointestinal (GI) endoscopies internationally with which to compare the prevalence of 0.27% that we found, we do have a report of a 1.2% prevalence rate found in autopsies (26). As in other series, this study found that gastric NETS occur twice as often among women as they do in men (27).

The finding of gastric NETs in 35% of the 44 cases of NETs pathologies found among all the pathologies processed at the Hospital El Tunal contrasts with the range of prevalence rates for stomach NETs of between 2% and 9% of all NETs usually reported in the literature. The usually reported prevalence rates are highest for NETs in the bowel, followed in order by bronchial NETs, NETs in the appendix and rectal NETs. This makes us emphasize again that, if gastric NETs are being detected on a daily basis, it is probably because of the expanding use of upper GI endoscopy.

The endoscopic diagnoses in this study were performed on patients who underwent the procedure for various reasons including dyspepsia, gastroesophageal reflux and other disturbances including anemia and nausea. As has happened in other studies, most of the tumors discovered were asymptomatic. In fact, they are usually discovered incidentally during endoscopic evaluations (11, 12).

In the present series, 95% of tumors were located in the proximal stomach (20% in the fundus, 75% in the corpus) and most were type I. These findings coincide with reports in the literature (11).

Our work is one of the largest series to demonstrate the greater effectiveness of endoscopic management of these tumors compared to surgery which was only used for one case (3.5%). This is significant when compared to the series of Gladdy (28) et al. in which surgery was used in 29% of cases and Borsch (29) which used surgery in 43% of cases.

In Table 3 we compare our study with the major series reported to date noting that the present study included 28 patients with type I NET gathered over only 5 years whereas Gladdy's series covered 22 years and two institutions while the Borsch series was in 24 institutions. In our series endoscopic treatment was used for 94.5% of all patients. Although follow up time has been shorter than in the other studies, the 4 year survival rate of 100% is similar.

Tabla 3. Series comparison of type I NET treatment.

Study	Number	Surgery	Endoscopic Tx	Follow-up months	Survival %
Gladdy	65	19	46	42	100
Borch	51	22	29	95	98
Dakin	18	10	8	NR	NR
Jordan	18	10	8	72	100
Schindl	16	7	9	70	100
Rindi	152	NR	NR	53	100
Series actual	28	1	27	32,5	100

NR: Not reported.

As shown in various published series (28-33) there is a tendency to continue to manage these patients with surgery. This study shows that it is not necessary to take these radical measures as advances in endoscopes and accessories, plus the experience gained in this field allows us to treat the vast majority of these lesions without recourse to surgery. While antrectomies may be useful for the management of these patients since resection of the area which produces G cells can eradicate the stimulus to ECL cells and thus eradicate the tumor, an antrectomy is not free of surgical risks. Since it is major surgery, we must also take into account the subsequent possibility of morbidity (34). There are two reasons antrectomies may not be useful for patient management. One is the risk of error since the distal stomach and part of the duodenum must be resected. A poorly performed antrectomy can cause persistent hypergastrinemia. In addition, ECLs may become autonomous and no longer depend on the stimulation of gastrin that leads to persistence or recurrence of NETs (35, 36). Finally, performance of a gastrectomy does not exclude the patient from endoscopic follow.

We believe that surgery should be reserved for only those cases which have lesions greater than 2cm. In these cases there are risks not only of invasion into deeper layers of the stomach (muscularis propria) but there are also greater risks of metastases and metachronous adenocarcinomas with NETs (28). Nevertheless, the probability that a NET will reach this size is low. The fact that a patient has multiple lesions should not be considered an indication for surgical because these lesions can be resected endoscopically in various stages as demonstrated by our work and the work of others (37).

Based on experience in managing this type of patients, we believe that the following approach should be used. Once a gastric NET has been identified and confirmed by immunohistochemistry, an endoscopy should be performed if the lesion is greater than one cm in order to rule out infiltration of the muscularis propria, lymph nodes or the celiac artery. Next, if the lesion is smaller than 20mm, a musectomy should be performed. Nevertheless, recent Japanese reports suggest that lesions up to 15mm are susceptible to mucosectomies. Moreover, they suggest that the lesions which are most susceptible to submucosal dissection are those have free and clear edges. This ensures lower rates of recurrence, although here we should note that most (but not all) of these studies were of treatment of gastric adenocarcinomas. In terms of technique, the physician should use the technique in which she or he has the most experience, although suction techniques using a cap or band can resect larger lesions.

Once resection of the lesion or lesions is complete, it is essential to review the pathology especially Antigen KI-67 levels. When they are lower 2%, the prognosis is excellent. The patient should return for a checkup in 3 to 6 months. If no lesions are found, annual checkups are recommended for the rest of the patient's life. When lesions are found at the first checkup, the re-resection protocol should be followed. At checkups, or when a lesion is larger than 2 cm, a gastric map of the patient should be made to rule out the possibility of gastric synchronous adenocarcinomas such as NETs.

It is not necessary to perform costly tests such as PET scans, CT scans and Octreoescans since the probability of metastasis is very low.

Recent studies also suggest that octreotide can be used for patients with multiple lesions without resorting to surgery or endoscopic resection. This sounds attractive when you consider that the antitumor effect of this substance has been demonstrated, but it is better to wait for longer-term follow-up studies before recommending its use.

CONCLUSIONS

This study, which identified 29 cases of gastric NETs, is a large series especially considering that it was conducted by only one group of researchers. Since most of these tumors were found incidental to endoscopy, it is very important that the endoscopist always keep in mind this possibility. Because these lesions are usually small, the inspection of the gastric mucosa must be done very carefully. If a diagnosis of a gastric NET is finally made. A pathologist must perform immunohistochemistry tests with chromogranin A and synaptophysin, as well as routinely determine the proliferation index of Ki-67. For lesions larger than 1cm endoscopy is needed to establish the lesion's depth and to decide upon endoscopic treatment based on this information. This endoscopic treatment is safe and effective as demonstrated by our work.

Conflicts of interest

None. The cost of this research was borne entirely by the researchers.

REFERENCES

1. Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, et al. Gastroenteropancreatic neuroendocrine tumors. Lancet Oncol 2008; 9: 61-72.
2. Modlin, IM, Lye, KD, Kidd, M. A 50-year analysis of 562 gastric carcinoids: small tumor or larger problem? Am J Gastroenterol 2004; 99: 23.
3. Lubarsch O. Uber den primaren Krebs des Ileum nebst Bemerkunge uber das gleichzeitige Vorkommen von Krebs und Tuberkulose. Virchows Arch 1888; 3: 280-317.
4. Oberndorfer S. Karzinoide Tumoren des Dunndarms. Frank Z Pathol 1907; 1: 426-429.
5. Burkitt, Pritchard. Review article: pathogenesis and management of gastric carcinoid tumors. Aliment Pharmacol Ther 2006; 24: 1305-1320.
6. Solcia E, Klöppel G, Sobin LH. Histological Typing of Endocrine Tumors: In Collaboration with 9 Pathologists from 4 Countries. Berlin, New York: Springer, 1999.
7. Gilligan CJ, Phil M, Lawton GP, Tang LH, West AB, Path MRC, Modlin IM. Gastric Carcinoid Tumors: The Biology and Therapy of an Enigmatic and Controversial Lesion. Clinical Reviews. Am J Gastroenterol 1995; 90: 338-52.
8. Mulkeen A, Cha C. Gastric carcinoid. Curr Opin Oncol 2004; 17: 1-6.
9. Alhman H, Wangberg B, Nilsson O. Aspects on diagnosis and treatment of the foregut carcinoid syndrome. Scand J Gastroenterol 1992; 27: 459-71.
10. Varas MJ. Neuroendocrine tumors –fascination and infrequency. Rev Esp Enferm Dig 2009; 101: 195-208.
11. Massironi S, Sciola V, Spampatti MP, Peracchi M, Conte D. Gastric carcinoids: between underestimation and overtreatment. World J Gastroenterol 2009; 15: 2177-83.
12. Borch K, Skarsgard J, Franzen L, Mardh S, Rehfeld JF. Benign gastric polyps: morphological and functional origin. Dig Dis Sci 2003; 48: 1292-7.
13. Castaño R, Ruiz MH, Jaramillo P, Sanín E, Botero ML, Cárdenas A, Juliao F, Erebrie F. Pólipos gástricos: aspectos epidemiológicos y su relación con el consumo de bloqueadores de bomba. Rev Col Gastroenterol 2005; 20(4): 48-59.
14. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer. 2003; 97: 934-959.
15. Borch K, Ahrén B, Ahlman. Gastric carcinoids: biologic behavior and prognosis after differentiated treatment in relation to type. Ann Surg 2005; 242: 64-73.
16. Havu, N. Enterochromaffin-like cell carcinoids of gastric mucosa in rats after life-long inhibition of gastric secretion. Digestion 1986; 35(Suppl 1): 42.
17. Rindi G, Bordi C, Rappel S. Gastric carcinoids and neuroendocrine carcinomas: pathogenesis, pathology and behavior. World J Surg 1996; 20: 168-72.
18. Pinchot SN, Holen K, Sippel RS, Chen H. Carcinoid tumors. Oncologist 2008; 13: 1255-69.
19. Gilligan, CJ, Lawton, GP, Tang, LH, et al. Gastric carcinoid tumor: The biology and therapy of an enigmatic and controversial lesion. Am J Gastroenterol 1995; 90: 338.
20. Sippel RS, Chen H. Carcinoid tumors. Surg Oncol Clin N Am 2006; 15: 463-78.
21. Solcia E, Fiocca R, Villani L, Luinetti O, Capella C. Hyperplastic, dysplastic, and neoplastic enterochromaffinlikecell proliferations of the gastric mucosa. Classification and histogenesis. Am J Surg Pathol 1995; 19 (Suppl 1): S1-S7.
22. Clemente C, Puig V, Mirada A. Tumor carcinoide. Análisis de 131 casos. Rev Clin Esp 1994; 194: 291-3.
23. Gómez M, Otero W, Arbeláez V. Tratamiento endoscópico de cáncer gástrico temprano en Colombia con seguimiento a cinco años. Rev Col Gastroenterol 2009; 24: 347-352.
24. Scherubl H, Cadiot C, Jensen RT, Rosch T, Stolzel U, Klopel G. Neuroendocrine tumors of the stomach (Gastric carcinoids) are on the rise: small tumors, small problems? Endoscopy 2010; 47: 664-71.
25. Ellis L, Shale MJ, Coleman MP. Carcinoid Tumors of the Gastrointestinal Tract: Trends in Incidence in England Since 1971. Am J Gastroenterol 2010.
26. Modlin IM, Lye KD, Kidd M. Carcinoid tumors of the stomach. Surg Oncol 2003; 12: 153-72.
27. Hou W, Schubert ML. Treatment of gastric carcinoids. Curr Tr Opt Gastroenterol 2007; 10: 123-33.
28. Gladdy R, Strong V, Coit D, Allen P, Gerdes H. Defining Surgical Indications for Type I Gastric Carcinoid Tumor. Ann Surg Oncol 2009; 16: 3154-3160.
29. Borch K, Ahren B, Ahlman H, et al. Gastric carcinoids: biologic behavior and prognosis after differentiated treatment in relation to type. Ann Surg 2005; 242(1): 64-73.
30. Dakin GF, Warner RR, Pomp A, et al. Presentation, treatment, and outcome of type 1 gastric carcinoid tumors. J Surg Oncol 2006; 93(5): 368-72.
31. Jordan PH Jr, Barroso A, Sweeney J. Gastric carcinoids in patients with hypergastrinemia. J Am Coll Surg 2004; 199(4): 552-5.
32. Schindl M, Kaserer K, Niederle B. Treatment of gastric neuroendocrine tumors: the necessity of a type-adapted treatment. Arch Surg 2001; 136(1): 49-54.
33. Rindi G, Azzoni C, La Rosa S, et al. ECL cell tumor and poorly differentiated endocrine carcinoma of the stomach: prognostic evaluation by pathological analysis. Gastroenterology 1999; 116(3): 532-42.
34. Hirschowitz BI, Griffith J, Pellegrin D, Cummings OW. Rapid regression of enterochromaffinlike cell gastric carcinoids in pernicious anemia after antrectomy. Gastroenterology 1992; 102(4Pt 1): 1409-18.
35. Guillem P, Vlaeminck-Guillem V, Leteurtre E, et al. Fundic endocrine tumors and atrophic gastritis: the value of antrectomy. Gastroenterol Clin Biol 2002; 26(8-9): 782-5.
36. Wangberg B, Grimelius L, Granerus G, et al. The role of gastric resection in the management of multicentric argyrophil gastric carcinoids. Surgery 1990; 108(5): 851-7.
37. Ichikawa J, Tanabe S, Koizumi W, et al. Endoscopic mucosal resection in the management of gastric carcinoid tumors. Endoscopy 2003; 35(3): 203-6.