Gastroenteropancreatic neuroendocrine tumors (GEP-NETS)

Cristian Camilo Vargas Martínez, MD,[1] Rodrigo Castaño Llano, MD.[2]

[1] Medical Student, Universidad de Antioquia, Medellín, Colombia. Gastrohepatology Group. Universidad de Antioquia. Medellín, Colombia. email: crivargas@gmail.com

[2] Gastrointestinal Surgeon and Endoscopist, Hospital Pablo Tobón Uribe, Medellín, Colombia. Professor of Surgery, Universidad Pontificia Bolivariana. Medellín, Colombia. Gastrohepatology Group. Universidad de Antioquia, Medellín, Colombia.

Received: 27-10-09
Accepted: 26-05-10

Abstract

Gastroenteropancreatic neuroendocrine tumors (GEP-NETS) are rare neoplasms which can occur anywhere in the gastrointestinal tract. Their particular characteristics include uptake of silver salts, neuroendocrine cell marker expression and hormonal secretory granules. Depending on their size, anatomical location and upon whether or not metastasis has occurred, these tumors can show different clinical patterns and have different prognoses. Early diagnosis is essential for treating these lesions and improving the patients' prognoses, but it requires a high degree of suspicion and confirmation by special testing. Surgical treatment is the first choice, but other medical therapy can be helpful for patients who have unresectable disease. This review presents the most relevant aspects of classification, morphology, methods of locating tumors, diagnosis and treatment of GEP-NETS. It presents only the Colombian experience in the epidemiology and management of these tumors.

Key words

Gastroenteropancreatic neuroendocrine tumors (GEP-NETS), carcinoid tumor, carcinoid syndrome, gastrinoma.

INTRODUCTION

The diffuse endocrine system (DES) of the gastroenteropancreatic (GEP) tract represents the amplest system of the entire organism (9) with at least 16 different endocrine cells that produce more than 50 different amines or peptides (10, 11). Neuroendocrine tumors (NETs) are considered to have malignant potential and can be indolent until they become clinically noticeable through metastasis or manifestations of carcinoid syndrome (5, 8). Although it was recognized at the end of the 19th Century, it was not until 1907 that Oberndorfer (4) coined the term *carcinoid tumor* (CT) to differentiate these less aggressive neoplasias from carcinomas. Thorson & Waldestrom's group (6) group was the first to describing a series of patients with ileal CT and hepatic metastases who presented the so-called carcinoid syndrome. They found diarrhea, asthma, face flushing, cyanosis and right valvular lesions. Several reports related the genesis of this syndrome to the endocrine cells. These tumors represent less than 1% of all neoplasias, although recent evidence suggests there has been an increase in their incidence (8).

NOMENCLATURE AND CLASSIFICATION

The historical term *carcinoid tumor* is becoming more and more unsuitable for grouping tumors with neuroendocrine characteristics. At present, it is reserved only for benign tumors and serotonin producing lesions (9, 11). Another disadvantage with the use of the carcinoid term is associated with the presentation of the carcinoid syndrome (CS) in certain types of tumors, such as enterochromaffin cells (EC). They produce vasoactive substances such as serotonin and substance P, whereas carcinoids without EC are associated with other types of syndromes or are more frequently silent (13). The NET term covers a wide spectrum of these neoplasias from the classic presentation of the carcinoid tumor on one side to the anaplastic variety

on the other. The new classification aims to group tumors according to their site of origin (foregut, midgut and hindgut for gastrointestinal varieties). The second principle is to subdivide them in relation to their biological behavior:

1. Benign behavior.
2. Uncertain behavior. These tumors may be benign or have a low degree of malignity.
3. Tumors with low degree of malignity.
4. Tumors with high degree of malignity.

The main criteria for this last denomination are histological differentiation, angiolymphatic invasion, direct invasion of neighboring organs and the presence of metastasis. Another criterion which has become an important parameter is the size. A third principle in classification is incorporation of the hormonal function and its designation as functioning or non-functioning (12). This classification does not consider tumors with mixed characteristics such as endocrine-exocrine (also called amphicrine). These tumors exhibit different lines of cellular differentiation. Those initially described were in the appendix and were named carcinomas of the calciform cells. Mixed neoplasias, adenocarcinomas focused on neuroendocrine cells, must be considered as a separate group because their biological behavior is determined mainly by the content and differentiation of their exocrine component (14). The currently accepted classification of these tumors is presented in Table 1.

HISTOGENESIS

Peculiar histochemical characteristics related to the argentaffin and argyrophilic reactions of the cells of the neuroendocrine system can be detected using light microscopy. Enterochromaffin (EC) cells are the most common endocrine cells in the intestine. They can be found throughout the intestines, although not in the esophagus. In the intestine they are concentrated in the duodenum, terminal ileum and appendix. According to Pearse (7) they all share the characteristic of being able to capture amine precursors and decarboxylate them. The extraction of numerous neuroendocrine peptides and the availability of different immunohistochemical methods make it possible to identify where they are synthesized and stored (15).

Williams and Sandler (17) have classified these tumors according to place of origin: foregut (irrigated by the celiac trunk), midgut (irrigated by the superior mesenteric artery) and hindgut (irrigated by the inferior mesenteric artery). The endocrine tumors of the pancreas and lungs behave like those of the foregut. This has allowed us to understand the hormonal behavior of these neoplasias.

MORPHOLOGY

The neoplasias with cells that directly capture and deposit silver salts are called argentaffin. These neoplasias are related to

Table 1. NET classification according to the World Health Organization (WHO) (15).

Location	Well differentiated endocrine tumor		Well differentiated endocrine carcinoma	Badly differentiated endocrine carcinoma
	Benign Behavior	Uncertain Behavior		
Pancreas	< 2 cm <2 mitosis* <2% Ki67 No vascular invasion	≥ 2 cm > 2 mitosis > 2% Ki67 Vascular invasion	Local invasion 2-10 mitosis >5% Ki67 Vascular invasion and metastasis	Small cells > 10 mitosis > 15% Ki67 Vascular and perineural invasion
Stomach	Mucosa/Submucosa ≤ 1 cm No vascular invasion	Mucosa/Submucosa > 1 cm Vascular invasion	Invasion to muscularis propia Metastasis present	Small cells
Duodenum/Jejunum	Mucosa/Submucosa ≤ 1 cm No vascular invasion	Mucosa/Submucosa > 1 cm Vascular invasion	Invasion to muscularis propia Metastasis present	Small cells
Ileum/Colon/Rectum	Mucosa/Submucosa ≤ 1 cm (ileum) ≤ 2 cm (colon) No vascular invasion	Mucosa/Submucosa > 1 cm (ileum) > 2 cm (colon) Vascular invasion	Invasion to muscularis propia Metastasis present	Small cells
Appendix	≤ 2 cm No vascular invasion	> 2 cm Vascular invasion	Invasion to the mesoappendix Metastasis present	Small cells

*Number of mitoses in 10 high power fields.

aggressive behavior. Neoplasias that require an external agent to acquire and deposit these salts are called argyrophilic, and they display a more benign behavior. Tumors of the foregut are more frequently composed of argyrophilic cells. Those of the midgut are the most aggressive and are composed almost exclusively of argentaffin cells. NET of the hindgut present cells with both characteristics. Nevertheless, the cause of the very different biological behaviors of neoplasias in the appendix and the ileum is not known, even though both are in the midgut and are predominantly argentaffin cells. Immunohistochemical detection of different markers from the neuroendocrine cells (neuronal specific enolase (1), chromogranin (2), synaptophysin (3)) allows for differentiation of endocrine and non-endocrine tumors. This is done in combination with silver staining. Immunohistochemistry has shown that tumors of the foregut present a greater hormonal load than other tumors. Carcinoid syndrome frequently occurs in tumors of bronchial tree, pancreas, duodenum or proximal jejunum (foregut). Gastric NETs are frequently asymptomatic, argyrophilic and rarely display cells with serotonin grains. NETs dependent on gastrin originating in an environment of atrophic gastritis are benign, whereas those which are not dependent on gastrin are potentially malignant (15, 16).

The ultrastructure of GI tract neuroendocrine cells was defined even before the appearance of immunohistochemistry. Secretory granules are characteristic of NETs. The typical histological frame consists of a focal point of small, regular, pallisaded cells. An atypical form has noticeable pleomorphisms, irregular and hyperchromatic nuclei, high numbers of mitoses and areas of necrosis. This form relates it to a worse prognosis.

Unlike the great number of hormones of the cells of the foregut, tumors of the midgut present a smaller variety of neuroendocrine cells. They mainly produce serotonin and tachykinin, which can serve as tumoral markers (15). NETs in the hindgut present a large amount of cells which produce peptides such as somatostatin, enkephalin, substance P, serotonin, and even insulin. Considering the fact that tumors of the midgut produce fewer hormones by than those of the foregut and hindgut, production of hormones is not a prognostic parameter (18).

DISTRIBUTION AND PROGNOSIS

85% of NETs originate in the gastrointestinal tract, 10% in the lungs (mainly as bronchial carcinoids) and the rest in the larynx, thymus, kidney, ovary, prostate, and skin. The most frequent location in the gastrointestinal tract is in the appendix followed by the rectum and the ileum (Table 2). In CAT scans the clinical presentation varies according to anatomical location. Survival depends primarily on tumor size (influenced by rate of growth and degree of differentiation) and upon whether or not the tumor has metastasized. The principal sites of metastases are lymph nodes, the mesentery, liver, lungs and peritoneum. To a lesser degree survival depends on the location of the tumor. The survival rate is 99% for lesions in the appendix, independent of their state, but it is only 75% for lesions located in the small intestine, and it diminishes to 54% when all states are considered.

Table 2. NET distribution according to location (n=2837) (19).

Location	%
Appendix	44
Rectum	15
Ileum	11
Lungs and Bronchus	10
Small intestine (non- specific)	5
Colon	5
Cecum	3
Stomach	2
Duodenum	2
Jejunum	1

In general terms, these are good prognoses for this type of lesion. This agrees with the appreciation of Oberdonfer (4) regarding carcinoids. Given the limitations on endoscopic and radiological evaluation of NETs of the small intestine, the recent use of imaging through nuclear medicine is a good alternative. The majority of NETs have somatostatin membrane receivers. Octreotide, an analog of somatostatin with prolonged survival is frequently used in hormone therapy in patients with SC or diarrhea. In various studies, octreotide has been marked with Indium 111 or Technetium 127 and used to locate tumors with positive receivers for somatostatin. This technique allows for early detection and more precise stratification of these neoplasias, moreover it provides important therapeutic information about which tumors will respond to hormone treatment (20).

Esophageal NETs

Esophageal NETs are rare. They exhibit the morphology of the neoplasia of small lung cells. Their flaky or glandular differentiation has also been varyingly described. They are found in the third distal as big vegetating, ulcerated, fast growing masses. This accounts for the poor prognoses associated with these tumors (18).

Gastric NETs

According to a review by Godwing (19), gastric NETS represent 4% of the neoplasias in the gastrointestinal tract.

They have been classified according to their relation to states of hypergastrinemia or based on chronic atrophic gastritis. When chronic atrophic gastritis is present, with or without pernicious anemia, NETs are classified as type I. When NETS are associated with Zollinger Ellison syndrome, or are combined with type 1 multiple endocrine neoplasias (MENs), they are classified as type II. Sporadic forms are grouped together as type III (Figure 1).

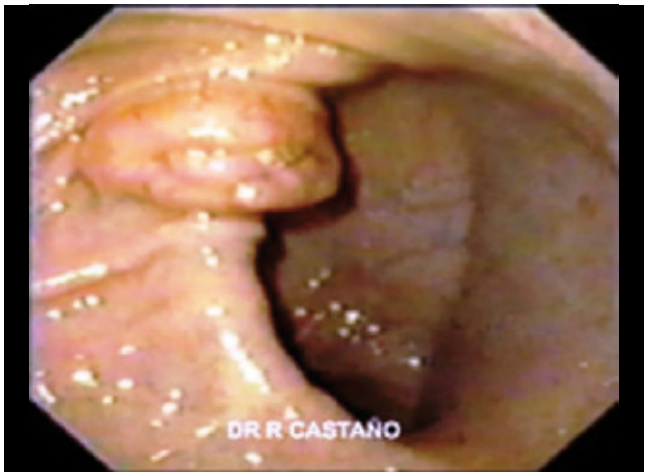

Figure 1. Gastric NET associated with chronic antral gastritis.

These distinctions have implications for outcomes because tumors associated with chronic atrophic gastritis, MEN 1 or Zollinger Ellison syndrome have better prognoses than do sporadic forms. Most of these tumors are small, well-differentiated and are confined to the mucosa and submucosa of the fundus, corpus or the corporal-antral transition. They manifest as benign polypoid lesions. They are mainly composed of argyrophilic cells with histamine production. Frequently they are multi-centric and are associated with chronic atrophic fundic gastritis (CAFG). Through autoimmune destruction of the parietal cells profound hypochlorhydria with hypergastrinemia can develop. Frequently pernicious anemia also develops. This presentation, which represents 2/3 of all gastric NET, is accompanied by hyperplasia of ECs. In a series of 27 patients with NET associated with chronic atrophic gastritis with diameters up to 2cm, none had metastasized. A review of the literature showed ganglion compromise in only 8.6% of these case (21). They have been also associated with prolonged consumption proton pump inhibitors (PPIs) (22). The combination of Zollinger Ellison syndrome with MEN 1 is accompanied by hypergastrinemia that leads to hyperplasia of ECs. This induces to tumor development. These tumors are characteristically small (< 1 cm on average) but metastasize to the lymph nodes. The sporadic forms are larger (greater than 2 cm) with angiolymphatic invasions or complete wall penetrations. More than 60% metastasize, with hepatic metastases in up to 50% of the cases of sporadic forms. Survival time varies between 2 and 4 years. They can produce histamine and cause CS. These tumors, which account for 20% of stomach NETs appear as a solitary mass in which ECs predominate. G cell tumors are rare and are located in the pyloric antrum. The poorly differentiated forms are constituted by intermediate size cells instead of small cells. 25% of these patients survive for one year. The foregoing suggests that tumors smaller than 1 cm are usually benign. Tumors between 1cm and 2 cm which appear with chronic atrophic gastritis or with MEN-1 and/or Zollinger Ellison syndrome and hypergastrinemia, whether the tumors are single or multiple, are difficult to predict but generally well located. Tumors bigger than 2 cm are malignant and frequently develop metastases. The undifferentiated forms have poor prognoses regardless of their size (23).

Pancreatic NETs

Pancreatic NETs can have the typical symptoms of hormonal hypersecretion including insulinoma, gastrinoma, VIPoma, glucagonoma or somatostatinoma. Up to 50% are non-functioning or secrete peptides of low biological power such as pancreatic polypeptide (PP) or neurotensin. The remaining 50% of pancreatic NET cases may have metastasized at the time of diagnosis (24). Insulinomas and gastrinomas are the most frequent. 90% of these insulinomas are benign, smaller than two cm and are single neoplasias. 6% to 13% are multiple neoplasias. 4% to 6% are associated with MEN-1. They are characterized by hypoglycemia with neuroglycopenic symptoms. The release of catecholamine induced by hypoglycemia generates sweating, tremors and palpitations. The chronic secretion of gastrin in gastrinomas leads to elevated gastric acid production, the appearance of peptic ulcers, severe and refractory diarrhea, and gastroesophageal reflux. At the time of diagnosis, 50% to 60% of gastrinomas are malignant. These tumors are most frequently located in the pancreas (24% to 53%) or the duodenum (13% to 49%). 20% of gastrinomas are MEN-1. VIPomas secrete vasoactive intestinal peptide and produce Verner Morrison syndrome which is characterized by large volumes of watery diarrhea, hypokalemia and dehydration. They are rare, usually large (72% are larger than 5 cm) and malignant (64% to 92%) at the time of the diagnosis. Extra-pancreatic VIPomas occur more frequently in children and are of neurogenic origin (ganglioneuromas, ganglioneuroblastomas, neuroblastomas and pheochromocytomas) (24).

Glucagonomas are rare. They measure from 5cm to 10 cm, and 50% to 82% are metastatic at the time of diagnosis. They most frequently present with necrolytic migratory

erythema and are associated with diabetes, anemia, loss of weight, depression, diarrhea and thromboembolism (25). Somatostatinomas are the rarest. They also originate in the duodenum or the ampulla of Vater. They can be part of neurofibromatosis type I. Pancreatic tumors are big, and 70% to 92% are metastatic. In the clinic they are found with diabetes, cholelithiasis, diarrhea with steatorrhea, hypochlorhydria, abdominal pain, loss of weight and anemia. 30% to 50% of these tumors are non-functioning. They must be well-differentiated from pancreatic adenocarcinomas because the implications for outcomes are very different. Generally, those associated with MEN-1 are big and multifocal. 62% to 92% are malignant (27).

Duodenal NETs

Duodenal NETs occur less frequently comprising only 1% to 2% of this group of neoplasias. 5 types have been recognized:

1. Gastrin producers
2. Somatostatin producers
3. Paragangliomas
4. Calcitonin, serotonin and pancreatic polypeptide producers
5. Undifferentiated

Unlike NETs in the stomach, where the prognosis depends more on the size and association with other entities, in the duodenum the evolution of NETs depends on size and functional characteristics. 60% of these tumors are gastrin producers, while one third are associated with Zollinger Ellison syndrome and are type 1 MENs. 40% of those with Zollinger Ellison syndrome have duodenal gastrinoma while the other 60% have a tumor located in the pancreas. 90% of patients with both MEN-1 and Zollinger Ellison syndrome have duodenal gastrinomas which are most frequently multi-centric and located in the first and second portions of the duodenum. They appear as submucous nodules that can easily go unnoticed in an endoscopy. Although small, they are mainly functioning tumors which frequently metastasize to nearby lymph nodes. These metastases are frequently larger than the primary tumor. Invasion of the liver is rare and late occurring. Non-functioning forms are more frequently located in the duodenal bulb (28). Somatostatin producers represent 15% to 20% of these neoplasias. They occur almost exclusively in the ampulla of Vater and appear as prominent masses. Histologically they appear with a glandular pattern and psammoma bodies. At the time of diagnosis the majority show muscular invasion and ganglionic metastases. Nevertheless, they are non-functioning unlike their counterparts in the pancreas. One third are associated with Bon Recklinghausen disease (neurofibromatosis type 1). Paragangliomas are located in the area of the ampulla or peri-ampulla and are third in frequency. They primarily present somatostatin and pancreatic polypeptide. Frequently they are bigger than 2 cm and have compromised the muscle at the time of diagnosis. They are not always benign (29). Tumors that produce serotonin, calcitonin or PP are rare. They are usually located away from the ampulla with no signs of invasion. Carcinoid appearance is exceptional. The majority of these tumors are well differentiated, benign and non-functioning. Undifferentiated forms are rare and more frequently affect the ampulla of Vater (Figure 2).

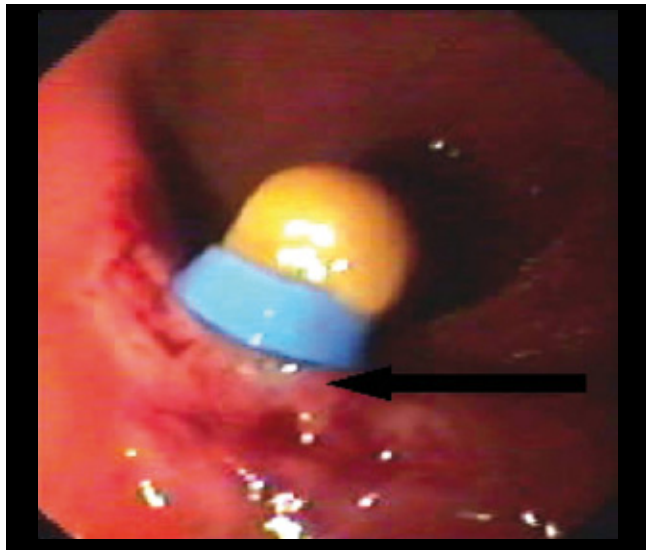

Figure 2. Duodenal NET managed with endoscopic bands.

Jejunoileal NETs

Jejunoileal NETs account for between 20% and 30% of NETs in the GI tract. The majority are argentaffin. Mainly located in the distal ileum, they are EC composites that produce serotonin and substance P. They appear as yellow-grayish nodules in the submucosa. Symptomatic cases are larger than 1 cm, with invasions into the mesenterium, local fibrosis and angulation of the intestine which can lead to intestinal obstruction. Jejunoileal NETs larger than 2 cm are malignant and almost always appear with ganglionic metastasis. 40% of these neoplasias are multiple. In 20% of the malignant forms they are associated with SC, which implies the development of hepatic metastasis. Tumors which are bigger than 2 cm which compromise tissue beyond the submucosa, are angio-invasive and have CS are extremely malignant. Undifferentiated forms are rare (8) (Figure 3).

NETs in the Appendix

In 3 to 9 out of every 1,000 appendectomies NETS are found, but they are generally benign. They account for 50%

of abdominal NETs. Similar to ileal NETs, they are frequently argentaffins with ECs and produce serotonin and substance P. 70% are located at the end of the appendix and are smaller than 2 cms. Recently, analysis of positive staining for protein S-100t has been cited to support the hypothesis that these tumors originate from epithelial neuroendocrine complexes rather than from intraepithelial endocrine cells. The second most common form of NETs in the appendix is composed of argyrophilic cells and produces peptides such enteroglucagon, PP and PYY. Generally they present good prognoses with metastases occurring in between 1.4% and 8% of all cases. Those that metastasize are generally bigger than 2 cm. Invasion of the mesoappendix, independent of tumor size, is a clear marker of metastasis. Tumors in the base of the appendix that compromise the resection margin require hemicolectomy to avoid leaving any residual tumor and a future relapse. SC is extremely rare in these neoplasias. Its discovery suggests that it has metastasized to the liver and/or retroperitoneum (30).

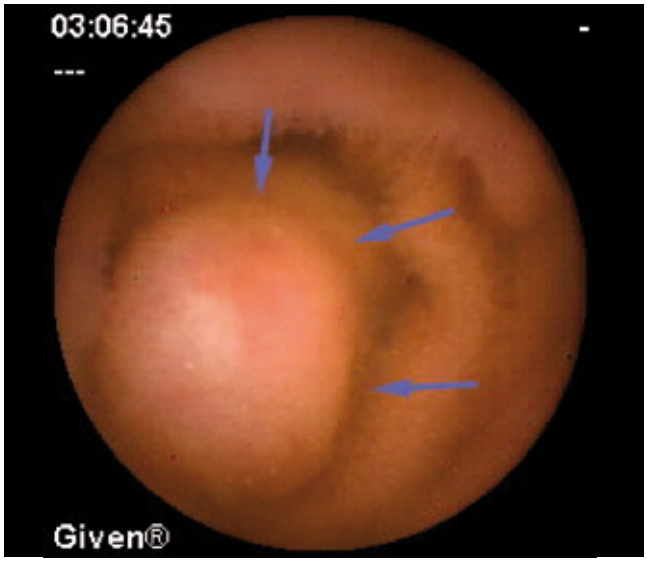

Figure 3. Ileal NET found by capsule endoscopy.

Colorectal NET

Three types of colorectal NETs have been described: those composed of argyrophilic cells, EC producers of serotonin and substance P and poorly differentiated (small cell) NETs (31). The well-differentiated argentaffins are frequently located in the rectum. They account for 10% of all these NETs. They are found incidentally in 1/2,500 proctoscopies. Frequently they are smaller than 1 cm and immunohistochemistry shows that they are positive for glucagon 29, glucagon 37, fragments of proglucagon, PYY, and PP. Less frequently we find serotonin, substance P, somatostatin, insulin, enkephalin, B endorphins, neurotensin, human gonadotropin hormone and motilin. Size is the main predicting factor for their behavior. The risk of metastasis for tumors smaller than 1 cm is smaller than 3%, but the risk increases to 7% for tumors between 1cm and 2 cm, and if there is invasion of muscular tissue it rises to 46%. Tumors 2 cm and larger metastasize in 78% of cases. Argentaffin forms producing serotonin predominate in the colon and in the cecum, where characteristically they are usually larger. However, those in the colon have a worse prognosis. SC appeared in 4 of 118. All of these presented hepatic metastases. Poorly differentiated forms present a mass of fast growth. No associated hormonal syndromes have been described. Average patient survival time is 5 months (Figure 4) (32).

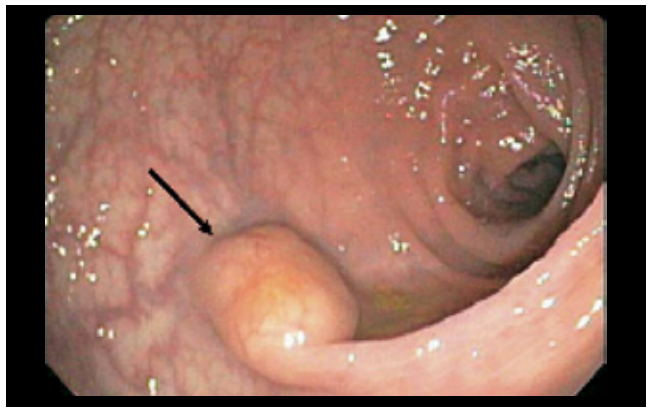

Figure 4. Upper rectum NET with intact mucosa.

DIAGNOSIS AND CLINICAL SYNDROMES

Different tumor markers in blood or urine have been used to diagnose and monitor NET. Among the generic markers are chromogranin A (CGA) a glycoprotein contained in EC secretion granules. It is the most important marker in blood (33). High levels have been observed in 60% to 80% of functioning and non-functioning NETs, but these high levels have also been observed in situations such as renal insufficiency, chronic atrophic gastritis, and PPI use in which no tumors are present (34). Other nonspecific markers include neuron- specific enolase, PP and chorionic gonadotropin hormone with less sensitivity and specificity than CgA11. 5-OH-indolacetic acid (5-HIA) is a specific marker for serotonin secreting tumors. It is a metabolite of serotonin that can be detected in urine after 24 hours. The sensitivity of 5-HIA is 65% to 75%, and its specificity is 90% to 100% (10, 11).

Characteristically, patients with carcinoid syndrome present increased serotonin deposits, increased levels of serotonin in platelets and increased levels of 5-HIA acid in urine. The diagnosis is confirmed if the increased excre-

tion of 5-HIA acid in urine of 24 hours exceeds 10 mgs. However, before samples are taken the patient should take the precaution to restrict consumption of serotonin rich foods such as bananas, grapes, pineapple, tomatoes, plums, eggplant, kiwi fruit and nuts for 3 to five days. The patient must also suspend cough syrups, levodopa, methysergide, paracetamol, NSAIDs, and caffeine for the same period. If these precautions are not taken falsely elevated results are likely. On the other hand, ACTH, steroids, heparin, isoniazid and phenothiazines give false negative results (11). For functioning NET, the dosage of specific hormones that cause the characteristic syndrome represents the specific marker. For patients suspected of insulinoma blood must be tested for glycemia, insulin, peptide C and pro-insulin. Prolonged fasting for 48 to 72 hours is the gold standard for diagnosis since 98% develop symptoms. For Zollinger Ellison syndrome testing for serum gastrin (> 1000 ng/L) and acid basal secretion with pH <2.5 establishes the diagnosis. A provocation test with secretin is performed on patients with gastrin levels lower than 1000 ng/L. Gastric or colon lesions can be evaluated by endoscopy or colonoscopy or by endoscopic ultrasound. Tumors of the small intestine have been evaluated by contrast radiological studies and more recently with enteroscopy and endoscopic capsules. For pancreatic tumors the CA T scans magnetic resonance imaging are important for defining the extension of the tumor, the presence of metastases, and for evaluating the patient's response to treatment. Both methods have sensitivities between 30% and 94% (35).

Metaiodobenzylguanidine (MIBG) study is another method to evaluate NET producers of catecholamines, such as pheochromocytomas and paragangliomas. MIBG is less sensitive than the OctreoScan for other NETs (36). The obstacle to the use of this method is that it is expensive and not available except in centers of reference for these tumors. Functional imaging tools such as the OctreoScan have a great impact on the management of patients. They provide tools for better staging of the disease, and for visualization of hidden lesions and metastases. They can also be used to evaluate patients for eligibility for treatment with the analog of somatostatin. Since more than 90% of carcinoid tumors have somatostatin receptors, they can be detected with OctreoScan which uses octreotide that is visible with Indium 111. The sensitivity of this method varies between% 80 and 100%. It is an excellent way to evaluate metastatic diseases and can be used to monitor patients' responses to treatment (47). This test is highly specific for lesions of 1 cm or more for 80% to 90% of NETs- The exception is insulinomas, in which only 50% have these receptors. OctreoScan also detects remote metastases with a sensitivity of 96% (10, 11). On the other hand, positron emission tomography (PET scan) for NETs has not shown itself to be useful because of their low metabolic activity except for highly proliferative tumors with poor differentiation. Despite the development of diagnostic methods for this entity, the clinical syndrome related to the hormonal overproduction is rarely recognized. In a series of 3,632 NET patients, 60 cases (1.6%) had with carcinoid syndrome. It has been suggested that the absence of symptoms is related to the production of inactive hormones (prohormones) or to rapid degradation of these agents in the tumor or in general circulation. In the case of production of neuropeptides like serotonin, it is assumed that the number of producing cells is so small that the amount that enters circulation is too small to manifest itself. Primary symptoms are facial flushing, diarrhea, abdominal pain and cardiac lesions followed by asthma and edema. The most characteristic of them is episodic facial flushing accompanied by periorbital or facial edema, oliguria, hypotension, and wheezing. The second most frequent manifestation is diarrhea, which goes from slight to explosive, but does not happen simultaneously with the episodes of facial flushing. This diarrhea is liquid and is explained by intestinal hypermotility. Occasionally episodes of bronchial constriction accompany facial flushing. Cardiac manifestations are delayed and occur by fibrosis of the right and/or left valvular tissue. A study with heart ultrasound showed that there was valvular compromise in 66% of the patients who developed carcinoid syndrome. Patients with valvular compromise present higher levels of tachykinin in blood and higher 5-HIA acid excretion in urine (8).

Currently, it is accepted that only part of CS can be explained by serotonin overproduction. Diarrhea seems to be produced when serotonin induces hypermotility and increases secretions in the jejunum. Consequently, the diarrhea can be controlled with serotonin blockers like methysergide, cyproheptadine and Ondansetron. These serotonin antagonists do not have major effects on facial flushing. Recently we have found high levels of tachykinin and substance P in the blood of patients with CS. This supports the theory of a multihormonal pathogenesis for these syndromes. We have even managed to reproduce the manifestations of face flushing minutes after the injection of substance P. Occasionally CS can occur without the presence of hepatic metastasis if venous drainage of the tumor to the circulatory system develops as in some ovarian or retroperitoneum NETs.

The presence or absence of hypergastrinemia can determine important aspects of a patient's prognosis and indicate therapy. Gough (37) found that of patients without hypergastrinemia, 66% developed metastases, 60% had increased 5-HIA acid, and 50% passed away as a result of the disease. On the other hand, patients with hypergastrinemia did not develop metastases or increase 5-HIA acid

levels, and did not die as the result of this disease. Instead, they displayed "typical" histological varieties.

NETs have been related to the presence of other non-neuroendocrine neoplasias. The rates of coincidence range between 46% and 55%. Most frequently these other neoplasias compromise the lungs, breasts, prostate and colon (38).

MEDICAL MANAGEMENT OF DISSEMINATED FORMS

Medical management of these lesions varies depending on whether they are well differentiated or badly differentiated lesions. Good differentiation produces CS. In these cases the immediate goal is to control the symptoms. As these lesions grow slowly, and patients' survival time is prolonged, we need to consider patient quality of life during treatment. Cyproheptadine blocks serotonin receptors 1 and 2 and H1 receptors for histamine. When it is administered in oral doses of 0.4 mg/kg/d three times a day, it diminishes diarrhea but not face flushing in patients with scattered NETs. Side effects include light sedation and dry mouths. Smaller numbers of patients experience uncontrollable nausea and vomiting which requires cessation of the treatment. Some studies have found regression of the tumor with this drug. However, this has not been reproduced in other series. The treatment of gastrinomas begins with the maximum permissible dose of omeprazole or lansoprazol (40-120 mg/d). Insulinomas are treated with diazoxide associated with hydrochlorothiazide. If they do not improve, calcium channel blockers, beta-blockers and steroids are recommended. With well differentiated forms interferon therapy with somatostatin analogs and directed therapy can be used. Somatostatin is a hormone that inhibits the secretion of several hormones and peptides. Somatostatin receptors appear in 70% to 95% of well differentiated NETs, with the major exception of insulinomas. Analogs of somatostatin allow control of symptoms associated with hormonal production and can be useful for preoperative treatment or treatment of inoperable tumors (27). They can be used as anti-proliferative agents. At high doses they can produce nearly 10% diminution in tumoral size and 50% stabilization of neoplastic growth. Two types of analogs have been used, octreotide and lanreotide. They bind primarily receptor subtypes 2 and 5. Recently, an analog called Pasireotide with affinity to all somatostatin receptor subtypes has been shown to be useful when other agents have failed (39). Somatostatin analogs such as octreotide are safe, easy to use, well tolerated, and only infrequently produce side effects. Side effects include abdominal pain, steatorrhea and cholelithiasis. Octreotide has been the most frequently used medication for scattered NETs. Not only does it have fewer side effects, it has also been shown to be remarkably effective at reducing urinary levels of 5-HIA acid, and at alleviating face flushing and diarrhea. Kvols (40) has also demonstrated that treatment with octreotide can result in regression of hepatic metastases, although the exact mechanism remains unknown. It has been suggested that there is a direct or indirect antineoplastic effect through inhibition of growth hormone, insulin and other growth factors. Alpha interferon has been used alone or in combination with octreotide to inhibit hormonal secretion and stabilize the disease. The response has been varied: 40% to 60% of those treated respond biochemically, while symptomatic improvement occurs in 40% to 70%, and diminution of tumoral volume results in 10% to 15% of these cases (41). Side effects are minimal, but include flu syndrome, fatigue, loss of weight, anemia, leukopenia and hepatotoxicity. Badly differentiated tumors require chemotherapy with streptozotocin, doxorubicin, dacarbazine, and 5-fluoruracile. When anaplasia is present, response to the use of etoposide and cisplatin varies between 40% and 70% (11). Since NETs express molecules such as epidermal growth factor and endothelial growth factor, new treatments including sorafenib, everolimus and mTOR inhibitors (Rapamycin) are now being used (9). Peptide receptor radionuclide therapy with the radiolabeled somatostatin analog has been used to take radioactivity to the interior of the tumor where they bind with the somatostatin receptors. Isotopes that have been used include 90Yttrium, 177Lutetium, 111 Indium. This treatment has been used for inoperable patients who have NETs with somatostatin receptors. Studies suggest stabilization of the disease in 50% to 70% of those treated, and control of symptoms for 70%. Doses have not yet been determined very well and have varied according to the different tolerances of the bone marrow, kidney or other organ treated (42).

SURGICAL MANAGEMENT

Surgery is the corner stone of NET treatment. It has been demonstrated that early surgery in these patients increases survival significantly. A study of prognoses of 195 patients with gastrinomas who were followed for 20 years showed that those patients who did not undergo surgery were 5 times more likely to develop metastases than those who had had their tumors resected. Also, patients who had not undergone surgery presented new lesions visible to imaging twice as frequently as the group which had undergone surgery. Finally, the NET related death rate was 23 times greater in the group of patients treated without surgery than in the group who were operated on (46).

Cytoreductive surgery can be carried out for 90% of the tumors in cases of local and regional compromise and for hepatic metastases. Palliative surgery should be performed in various situations. The primary tumor should be removed for patients with non-operable hepatic metastases, especially for hormonally functioning tumors. If the pri-

mary tumor is located in the small intestine and presents a high risk of obstruction, it should be removed. The tumor should be removed when surgery allows subsequent multimodal treatment. Surgery is indicated for the patients with scattered NETs when symptoms are incapacitating, but also in other situations. These include CS which is refractory to treatment; cases with episodic abdominal pain caused by intestinal obstruction, tumoral mass or vascular commitment; and patients with weight loss. Patients should be operated on early if resection is potentially curative or can reduce the necessity of medical therapy. CAT scans do not detect small tumors but aid in determination of the degree of local and distant extension. Ultrasound, simple abdominal x-rays, angiography, and contrast radiology provide very little additional information. For the 60% of NETs located in the appendix, when tumors are smaller than 2 cm, a simple appendectomy is curative. When lesions are slightly larger than 2 cm, appendectomies are also possible for older old patients and those with high surgical risks. Right hemicolectomy is reserved for young patients with lesions larger than 2 cm and who have with low surgical risks. In cases of tumors between 1 and 2 cm in which there is compromise of the mesoappendix or vascular invasion, more aggressive surgery is preferable, and resection of the cecum is recommended. These overall recommendations must be taken with reserve because tumors smaller than 1 cm can show evidence of muscular invasion, lymphatic permeation and compromise of periappendicular fat. These cases have long patient survival times without sequels even when they are only treated with a simple appendicectomy (8, 48).

Successful endoscopic treatment of stomach NETs has been reported. Criteria for endoscopic removal include tumors smaller than 2 cm, no histological signs of malignity, and presence of hypergastrinemia. NETs which cannot be totally removed or show invasion must be radically resected (43, 44).

Unfortunately, incidental findings of small intestinal NETs are minimal. If NETs are found, aggressive surgical removal in monoblock should be tried, but primary multicentric and other neoplasias must also be sought. 18% of these tumors have hepatic metastases. In spite of great tumoral mass, aggressive surgery is required. The most frequent tumor in Meckel's diverticulum is NET, and it presents the same ominous prognosis as do those in the ileum.

NET MANAGEMENT OF HEPATIC METASTASIS

The presence of hepatic metastasis implies a short patient survival time. Hepatic metastases almost always manifest with CS. Nevertheless, when tumoral growth is slow, patient survival time averages of 8.1 years after symptoms begin. The use of the octreotide controls some of CS symptoms. However, since large tumor size shows little response to medical therapy, we promulgate complete removal or at least efforts to obtain greater cytoreduction. Only 9% of symptomatic NETs are considered to be candidates for surgery. Palliative resection of the liver is recommended if at least 90% of the mass can be removed. Nevertheless, the number of patients whose symptoms are suitably alleviated and have good short term responses requires us to refine the indications for palliative surgery. Average patient survival time after intervention in cases of hepatic metastasis was of 218 months, compared to 48 months for patients without this intervention. Experience with liver transplants for these lesions is still scant, but transplants can be a good option for young patients with a controlled primary tumor and without extrahepatic tumoral compromise (10, 45). Embolization is preceded by angiography to determine permeability and hepatic portal vein anatomy. Clinically, patients follow a very predictable course after ligature or embolization. They develop pain in the right superior quadrant, fever, leukocytosis, plus altered and diminished hepatic function (increased AST and ALT). Although there are is no proof of any advantage of embolization with chemotherapy over the embolization alone, tumors larger than three cm respond better to radio frequency ablation combined with chemo-embolization (10). Even when there is multilobar compromise, laparotomy must not be discarded. By simply reducing the hepatic tumor mass, and resecting ischemic and obstructed intestinal segments, good palliation can be obtained. Also, prophylactic cholecystectomies must be performed to avoid gangrenous cholecystitis after ligature of the hepatic artery, embolization or prolonged administration of octreotide. The principal manifestations of intraoperative SC are facial flushing and hypotension after induction of the anesthesia. Support measures must be accompanied by administration of 50 mcg of octreotide, followed by another 50mcg after 15 seconds. This results in dramatic improvement. SC may occur at any time during surgery. Anesthesiologists should avoid thiopentone adrenergics, agonist releasers, noradrenaline, dopamine, succinylcholine and histamine (atracurium, d-Tubocurarine). Fentanyl and diazepam with vecuronium can be used to facilitate entubacion (8).

COLOMBIAN EXPERIENCE

The following previously published national experience evaluates the management and outcomes of these neoplasias in Colombia (8).

PATIENTS AND METHODS

This study was carried out at the National Institute of Cancerology, a third level center and site of reference for different neoplasias. 45,869 pathology reports from

between January 1 1988 and December 31 1992 were reviewed. 26 patients with NETs were found. 24 were chosen for strict follow-up monitoring. They included 10 men and 14 women with NETs in different abdominal locations. In all cases the tumor was diagnosed with either an endoscopic or surgical biopsy. Histological diagnoses were based on examination of hematoxylin-eosin stained tissue and, in some cases, with immunohistochemical phenotyping. The study was conducted in order to obtain a good analysis of patient survival time.

RESULTS

The average age of presentation was 60 years for men and 50 years for women. Locations did not coincide with those typical of series found in the literature. In those studies appendiceal NETs diagnosed as incidental findings predominate. Gastric NETs, with 9 cases (40%), predominated in this series. Proximal locations were most frequent (66%). In second place were rectal locations (20%). Those located in the right colon, esophagus, pancreas, duodenum and metastases of NET to the liver (with unknown primary tumors) represented 8% each.

The distribution of these neoplasias according to the classification of Williams and Sandler (17) was 62% in the foregut, 8% midgut, 22% hindgut and 2 cases (8%) of metastases to the liver (with primary tumors unknown). The average time that symptoms had developed before patients were seen at the institution was 11.5 months. Despite this greater numbers of recurrences and higher mortality rates were not found in these patients. Only one patient with CS (4.2%), presented NETs with multiple hepatic metastases with a primary tumor unknown origin. This patient had facial flushing, diarrhea, bronchial constriction and valvulopathy. Patient responded poorly to treatment with cyproheptadine. At that time octreotide was not used for treatment of SC crises. The patient's 24 hour 5-HIA acid level was 8.9 mg. The patient survived 8 months after an exploratory laparotomy in which peritoneal carcinogenesis with great tumoral compromise in the ileocecal union was found. 19 patients were resected with curative intentions. 13 of them survived for 55 months. One patient received only cytoreduction, 2 received palliation and 3 were declared to be unresectable. Overall patient survival time for the group of selected patients was 40 months. 5 patients who could not be operated on survived an average of 7 months (p 0.02). There were no significant differences related to tumor locations and patient survival times. No cases associated with multiple endocrine neoplasias were found in this review. 7 patients had distant relapses an average of 12 months after surgery, although no special predilection for any particular tumor location was found. Patient survival time after relapse was diagnosed was 7 months. Adjuvant chemotherapy was administered to 5 patients with 5-fluoruracil plus levamisole. 2 of them were combined with x-ray treatment. This was done for 3 gastric tumors and 2 colon tumors. X-rays were administered to 5 patients, 2 with stomach tumors, 1 with a tumor in the colon and 2 with rectal tumors. 13 patients died, 1 because of post-operative sepsis, 12 because of the disease. One patient is still alive after a relapse occurred in the liver.

DISCUSSION

This present series brings together experience with NET treatment at a center of reference, the National Institute of Cancerology in Bogota-Colombia. It emphasizes that over the 5 years from 1988 to 1992 26 cases were collected and 24 of them were monitored after treatment. Numbers for these patients were compared with figures recently reported for the country in a Latin American survey of NET treatment (36). That survey reported 150 cases of NET, including 83 gastrointestinal cases, which had been gathered over the 4 years from 2003 to 2006. This suggests an increase in incidence, but with a distribution similar to that reported in our series. This increase in incidence could be largely explained by the appearance of more sensitive and specific tests for detection of these tumors. These tests included enteroscopy, capsule endoscopy, OctreoScan plus better and more refined knowledge of pathological techniques such as immunohistochemistry. Patient survival time for these tumors is better than for similar carcinomas. Their indolent and insidious course allows for therapies that are otherwise rarely used. These include administration of Octreotide radiomarking in which radiomarked peptides bind with cell receptors, serving both for diagnosis and treatment. Patient survival time for the major hepatic resections that metastatic NETS frequently require has been improved. Two transplants have even been performed by the Gastro-hepatology group of the Universidad de Antioquia. One of them had a massive precocious relapse, but the other patient´s survival time was good. Several areas in local management of these lesions could be improved. These include expeditious availability of markers such as chromogranin A for blood and 5-hydroxyindoleacetic acid for urine. They also include availability of OctreoScan use which is expensive and difficult to obtain approval for from the leading health organizations. The best way to have a favorable impact on the prognoses of patients with these lesions is to develop interdisciplinary groups of specialists including oncologists, pathologists, endocrinologists, and surgeons who have a special interest in these tumors. This type of group exists today in Argentina and Brazil. They have developed a strategy of creating local registries to

allow for consolidated national tabulation and follow-up on these neoplasias. In addition to such national registries, it would be useful to have a consolidated Latin American registry for NETs.

REFERENCES

1. Lubarsh O. Uber den primären Krebs des Ileum nebst Bemerkungen über das glichzeitige Vorkommen von Krebs und tuberculose Virchow Arch 1888; 3: 280.
2. Ranson WB. A case of primary carcinorna of the ileum. Lancet 1890; 2: 1020.
3. Ciaccio C. Sur une nouvelle espèce cellulaire dans les glandes de lieberkühn. C R Soc Biol 1906; 1: 76.
4. Oberndorfer S. Karzinoide Tumoren des Dünndarms. Frankfrt Z Pathol 1907; 1: 407.
5. Lembeck F. 5-Hydoxytryptamine in a carcinoid tumor. Nature 1953; 172: 1910.
6. Thorson A, Bjork G, Bjorkman G. Malignant carcinoid of the srnall intestine with metastases to the liver, valvular disease of the right heart (pulmonary stenosis and tricuspid regurgitation without septal defect) peripheral vasomotor symptoms bronchoconstriction and an unusul type of cyanosis. Am Heart J 1954; 4: 795.
7. Pearse AGE. The cytochemistry and ultrastructure of polypeptide hormone producing cells of the APUD serics and the embryologic, physiologic and pathologic implications of the concept. J Histochem Cytochem 1969; 17: 303.
8. Castaño R, Aristizábal H, Hoyos S. Tumores neuroendocrinos abdominales. In: Botero M, ed. Cirugía. 2 ed. Medellín: Editorial Universidad de Antioquia 2002. p. 220-36.
9. Massironi S, Sciola V, Peracchi M, Ciafardini C, Spampatti MP, Conte D. Neuroendocrine tumors of the gastro-enteropancreatic system. World J Gastroenterol 2008; 14: 5377-84.
10. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 2008; 9: 61-72.
11. Ramage JK, Davies AH, Ardill J, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours. Gut 2005; 54 Suppl 4: iv1-16.
12. Kloppel G, Heitz PU, Capella C, Solcia E. Pathology and nomenclature of human gastrointestinal neuroendocrine (carcinoid) tumors and related lesions. World J Surg 1996; 20: 132-41.
13. Insabato L, Del Basso De Caro M, Caramanna E, De Rosa G. Pathology of neuroendocrine tumours. Front Biosci 2009; 14: 4712-8.
14. Faggiano A, Mansueto G, Ferolla P, et al. Diagnostic and prognostic implications of the World Health Organization classification of neuroendocrine tumors. J Endocrinol Invest 2008; 31: 216-23.
15. Solcia E, Klöppel G, Sobin LH. Histological Typing of Endocrine Tumors. WHO International Histological Classification of Tumors. 2 nd ed. Berlin: Springer; 2000: 56-70.
16. Rindi G, Kloppel G, Alhman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch 2006; 449: 395-401.
17. Williams ED, Sandler M. The classification of carcinoid tum ours. Lancet 1963; 1: 238- 9.
18. Chejfec G, Falkmer S, Askensten U, Grimelius L, Gould VE. Neuroendocrine tumors of the gastrointestinal tract. Pathol Res Pract 1988; 183: 143-54.
19. Godwin JD, 2nd. Carcinoid tumors. An analysis of 2,837 cases. Cancer 1975; 36: 560-9.
20. Hubalewska-Dydejczyk A, Fross-Baron K, Mikolajczak R, et al. 99mTc-EDDA/HYNICoctreotate scintigraphy, an efficient method for the detection and staging of carcinoid tumours: results of 3 years' experience. Eur J Nucl Med Mol Imaging 2006; 33: 1123-33.
21. Rindi G, Luinetti O, Cornaggia M, Capella C, Solcia E. Three subtypes of gastric argyrophil carcinoid and the gastric neuroendocrine carcinoma: a clinicopathologic study. Gastroenterology 1993; 104: 994-1006.
22. Castaño R, Ruiz MH, Jaramillo P, et al. Pólipos gástricos: aspectos epidemiológicos y su relación con el consumo de bloqueadores de bomba. Rev Col Gastroenterol 2005; 20: 25-34.
23. Hou W, Schubert ML. Treatment of gastric carcinoids. Curr Treat Options Gastroenterol 2007; 10: 123-33.
24. Alexakis N, Neoptolemos JP. Pancreatic neuroendocrine tumours. Best Pract Res Clin Gastroenterol 2008; 22: 183-205.
25. Marogy G, De Man M, Verslype C. Necrolytic migratory erythaema and glucagonoma syndrome. Acta Clin Belg 2009; 64: 70-1.
26. South CD, Baird MA, Marsh WL, Jr. Clinical challenges and images in GI. Ampullary somatostatinoma associated with neurofibromatosis type 1, presenting with iron-deficiency anemia. Gastroenterology 2009; 136: 51, 368.
27. Oberg K, Eriksson B. Endocrine tumours of the pancreas. Best Pract Res Clin Gastroenterol 2005; 19: 753-81.
28. Burke AP, Federspiel BH, Sobin LH, Shekitka KM, Helwig EB. Carcinoids of the duodenum. A histologic and immunohistochemical study of 65 tumors. Am J Surg Pathol 1989; 13: 828-37.
29. Selvakumar E, Rajendran S, Balachandar TG, et al. Neuroendocrine carcinoma of the ampulla of Vater: a clinicopathologic evaluation. Hepatobiliary Pancreat Dis Int 2008; 7: 422-5.
30. Moertel CG, Weiland LH, Nagorney DM, Dockerty MB. Carcinoid tumor of the appendix: treatment and prognosis. N Engl J Med 1987; 317: 1699-701.
31. Tsukamoto S, Fujita S, Yamaguchi T, et al. Clinicopathological characteristics and prognosis of rectal well-differentiated neuroendocrine tumors. Int J Colorectal Dis 2008; 23: 1109-13.
32. Vilallonga R, Espin Basany E, Lopez Cano M, Landolfi S, Armengol Carrasco M. [Neuroendocrine carcinomas of the

colon and rectum. A unit's experience over six years]. Rev Esp Enferm Dig 2008; 100: 11-6.
33. Jansson AM, Rosjo H, Omland T, et al. Prognostic value of circulating chromogranin A levels in acute coronary syndromes. Eur Heart J 2009; 30: 25-32.
34. Campana D, Nori F, Piscitelli L, et al. Chromogranin A: is it a useful marker of neuroendocrine tumors? J Clin Oncol 2007; 25: 1967-73.
35. Rockall AG, Reznek RH. Imaging of neuroendocrine tumours (CT/MR/US). Best Pract Res Clin Endocrinol Metab 2007; 21: 43-68.
36. Costa F, Domenichini E, Garavito G, et al. Management of neuroendocrine tumors: a meeting of experts from Latin America. Neuroendocrinology 2008; 88: 235-42.
37. Gough DB, Thompson GB, Crotty TB, et al. Diverse clinical and pathologic features of gastric carcinoid and the relevance of hypergastrinemia. World J Surg 1994; 18: 473-9; discussion 9-80.
38. Tichansky DS, Cagir B, Borrazzo E, et al. Risk of second cancers in patients with colorectal carcinoids. Dis Colon Rectum 2002; 45: 91-7.
39. Ben-Shlomo A, Melmed S. Pasireotide--a somatostatin analog for the potential treatment of acromegaly, neuroendocrine tumors and Cushing's disease. I Drugs 2007; 10: 885-95.
40. Kvols LK, Martin JK, Marsh HM, Moertel CG. Rapid reversal of carcinoid crisis with a somatostatin analogue. N Engl J Med 1985; 313: 1229-30.
41. Frank M, Klose KJ, Wied M, Ishaque N, Schade-Brittinger C, Arnold R. Combination therapy with octreotide and alpha-interferon: effect on tumor growth in metastatic endocrine gastroenteropancreatic tumors. Am J Gastroenterol 1999; 94: 1381-7.
42. Kwekkeboom DJ, de Herder WW, Kam BL, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0, Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol 2008; 26: 2124-30.
43. Mashimo Y, Matsuda T, Uraoka T, et al. Endoscopic submucosal resection with a ligation device is an effective and safe treatment for carcinoid tumors in the lower rectum. J Gastroenterol Hepatol 2008; 23: 218-21.
44. Martínez-Ares D, Souto-Ruzo J, Varas Lorenzo MJ, et al. Endoscopic ultrasoundassisted endoscopic resection of carcinoid tumors of the gastrointestinal tract. Rev Esp Enferm Dig 2004; 96: 847-55.
45. Frilling A, Li J, Malamutmann E, Schmid KW, Bockisch A, Broelsch CE. Treatment of liver metastases from neuroendocrine tumours in relation to the extent of hepatic disease. Br J Surg 2009; 96: 175-84.
46. Norton J, Fraker D, Alexander H, Gibril F, Liewehr D, Venzon D, Jensen R. Surgery Increases Survival in Patients with Gastrinoma. Ann Surg 2006; 244: 410-419.
47. Khan M, Coleman E. Diagnosis and therapy of carcinoid tumors—current state of the art and future directions. Nuclear Medicine and Biology 2008; 35: S177-S191.
48. Modlin I, Kidd M, Latich I, Zikusoka M, Shapiro M. Current Status of Gastrointestinal Carcinoids. Gastroenterology 2005; 128: 1717-1751.