

POINT OF VIEW

Neuroendocrine tumors – fascination and infrequency

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ABSTRACT

In this article, I review and update of gastro-entero-pancreatic neuroendocrine tumors, which so much fascination have risen among healthcare providers on grounds of their infrequency, hormonal syndromes, and high survival rate, is performed based on references from the past fifteen years.

Key words: Neuroendocrine tumors. Neuroendocrine pancreatic tumors. Gastro-entero-pancreatic endocrine tumors. Carcinoid tumors.

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DEFINITION

Neuroendocrine tumors (NETs) or gastroenteropancreatic endocrine tumors (GEPETs) (2% of all gastrointestinal tumors) have their origin in tissues derived from the neural crest, neuroectoderm, and endoderm; 60-70% are carcinoid tumors, and 20-40% are found in the pancreas (NEPTs) (Tables I and II). Gastrointestinal tract

endocrine tumors other than carcinoid tumors may be gastrinomas, enteroglucagonomas, somatostatinomas, or non-functioning neuroendocrine tumors. Many of the data discussed herein have been taken from prior reviews (1-5).

INCIDENCE

In necropsies 0.5-1.5%, or even up to 5%, are NEPTs (1-2), many of them silent. They represent 1-3% of all pancreatic neoplasms.

In Europe, in the one community-based study carried out thus far, incidence is smaller than one case per 100,000/year – specifically, 0.32 per 100,000/year for carcinoid tumors and 0.2 per 100,000/year (2 per million/year) in the pancreas (6). Insulinoma and gastrinoma, the most common types, have an incidence of 1 new case per million people and year. Glucagonoma and somatostatinoma are least common (1 per 20 and 40 million/year, respectively) (Table II).

Carcinoids are twice as common in Afroamerican patients than among Caucasians (7).

In the USA (8), incidence approaches 5 per million/year for NEPT, 1.8 in women and 2.6 in men, but is increasing and may well reach 10 per million people/year, with a higher frequency between 40 and 60 years of age, and in women.

In our country the incidence of NEPT may be 0.08 per 100,000 inhabitants/year, or 1 new case every two years in Hospitalet de Llobregat (Barcelona).

GENETICS

Tumors may be sporadic, particularly carcinoids, or may develop in association with dominant autosomic syndromes (2) – locus 11q13 for MEN-1 – including multiple

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Table I. Carcinoid classification

<i>Origin</i>	<i>CS</i>	<i>Genetic change</i>	<i>Site</i>	<i>Silver salts</i>
Foregut	30% Atypical	C 11q13	Bronchial, gastric, duodenal pancreatic	Argyrophilic
Midgut	70%	C 18q, 18p	Cecum, appendix, Typical	Argentaffin + intestines
Hindgut	No	–	Rectal Left colon	Argentaffin – and argyrophilic

Bronchopulmonary tumors are most frequent. Most carcinoids are found in the lung and gastrointestinal tract (appendix and bowel).

Table II. TNE classification (modified from 15 and 22)

<i>Tumor</i>	<i>Hormone</i>	<i>Syndrome</i>	<i>Location</i>	<i>Malignity</i>	<i>I</i>
Carcinoid	Serotonin (5-HIAA)	SC: Flushing, Diarrhea, etc.	Digestivo: 70% Páncreas: 20%	95-100%	+3
Insulinoma	Insulin and pro I Diazóxido	Hipoglicemia NEM-1: 4-8%	Páncreas: 99%	-10%	1-2
Gastrinoma	Gastrin NEM-1: 12-22%	SZE: IBPs	Duodeno: 70%	60-90%	-1.5
Vipoma	VIP	VMS	Pancreas: 90%	40-70%	-0.2
Glucagonoma	Glucagon Diabetes	MNE +	Pancreas: 100%	50-80%	-0.1
Somatostatinoma SMS	Inhibitory S.	Pancreas: 55%	+70%	Rare	
PPoma	PP NEM-1: 0-21%	Non-functioning	Pancreas: 100%	+60%	1-2
GHRFoma	GHRF Lung: 54%	Acromegaly	Pancreas: 30%	+60%-	
ACTHoma	ACTH	Cushing S.	Pancreas: 10%	+95%	Rare
ADHoma	ADH	SIADH	–		
Parathyrinoma	PTHrP	Hypercalcemia	Pancreas: 100%	84%	Rare
Calcitoninoma	Calcitonin	Diarrhea	Pancreas	+80%	Rare
Neurotensinoma	NT	Diarrhea	Pancreas	–	
Pheochromocytoma	Catecholamines	HBP	Pancreas, etc.	–	
Ghrelinoma	Ghrelin etc.,	Hyperglycemia, Intestine	Pancreas	–	

I: Incidence of new cases/million population/year. Insulinomas and gastrinomas are most frequent: nearly 50%. Vipomas represent 8% of all NETs (5). Pancreatic glucagonomas represent 7% of all NETs (16). Somatostatinomas represent 6% of all NETs (17). There may be ectopic secretion of ACTH, GR, and HCG alfa and beta; +: is greater than; -: is less than.

endocrine neoplasm (MEN; types 1 and 2; a and b), von Hippel-Lindau disease (VHL), von Recklinghausen's neurofibromatosis, and tuberous sclerosis (5) (Table III).

MEN-2 results from a mutation in the RET proto-oncogene.

The risk for carcinoid development is also accounted for by genetic factors. Indeed, gastric NETs are increased in women with diabetes and a family history of cancer (9).

FUNCTIONING AND NON-FUNCTIONING TUMORS (NFNET)

NFNETs are diagnosed during routine ultrasonography (Fig. 1), CT scans for unexplained abdominal symptoms, or late-stage disease (70% greater than 5 cm).

Their frequency is 20-58%, and up to 90% when located in the pancreas (10-12).

Table III. Hereditary syndromes associated with NET (4)

Syndrome	Gen	Assoc. NET type
MEN 1	Menin 11q13	Gastrinoma, NFNET, insulinoma, other in 75%. Thymic (57)
MEN 2	RET	CMT and pheochromocytoma
Neurofibromatosis type I	Hamartin 17q11	Duodenal somatostatinoma, in 0-10%
VHL disease	pVHL 3q25	NFNET: 10-17%
Tuberous sclerosis	Tuberin	Rarely (-1%), NFNET, insulinoma and gastrinoma
Familial carotid paraganglioma?	11q	Secretes serotonin



Fig. 1. Sonographic cross-section of the pancreatic region showing an ovoid hypoechoic nodule almost 9 mm in size, and suggestive of NEPT.

Corte transversal sonográfica sobre el área pancreática, detectándose nódulo ovoideo hipoecogénico de casi 9 mm, sugestivo de TNEP.

Most (over 70%) are not really functioning, since they secrete substances such as PP, other peptides (PYY, ghrelin, etc.), NSE, CgA, or HCG, but none of these substances results in specific symptoms.

Functioning or secretory tumors (60%) may result in multiple hormone secretion (MHS) or be associated with MEN, with well-defined syndromes.

Except for insulinoma (less than 10%) many NETs are malignant (50-60% or higher, particularly NFNET) and result in nodal, hepatic (most commonly), bony (12%), pulmonary (4%), and cerebral metastases (Table II).

Overall survival at 5 years never exceeds 67% when all NETs are considered. WHO has recently issued a classification system for NETs: well-differentiated tumor, well-differentiated carcinoma, and poorly-differentiated carcinoma, according to histology, size, and proliferation indices; a TNM (tumor, node, metastasis) classification had also been proposed earlier (5).

CLINICAL SUSPICION

NEPTs that inappropriately secrete peptides and hormones (FNEPTs) result in specific clinical syndromes with guide symptoms (13-15). Thus, the development of acute and/or chronic hypoglycemia (guide symptom) should prompt suspicion for hyperinsulinism due to pancreatic insulinoma (Table II).

The emergence of abdominal pain, vomiting and diarrhea in a patient with ulcer, particularly when *Helicobacter pylori*-negative, should alert on the presence of Zollinger-Ellison syndrome (ZES) due to pancreatic or extrapancreatic gastrinoma (14).

Glucagonoma syndrome is characterized by necrolytic migratory erythema (NME) (52%) and diabetes (22%) (16); somatostatinoma and corticotropinoma are also accompanied by hyperglycemia.

Verner-Morrison syndrome (VMS) from vipoma presents with secretory diarrhea and hypokalemia (70-100%). Many NEPTs produce chronic diarrhea, but only vipoma and neurotensinoma lead to hypokalemic diarrhea.

The clinical "inhibitory" somatostatinoma syndrome combines diabetes with bladder disease, diarrhea and hypochlorhydria. Somatostatinoma may arise in the duodenum or pancreas, with malignancy in excess of 43% (17).

Flushing is a typical finding of carcinoid syndrome (CS) that develops in 10% of carcinoid tumors (Table IV).

Clinical suspicion should lead physicians to order a hormone panel (MHS and MEN should also be ruled out), but on occasion tumors are non-functioning or hormone levels are within the normal range, and recourse to hormone provocation tests is required (14,15,18).

BIOCHEMICAL DIAGNOSIS

Pancreatic polypeptide (PP), neuron-specific enolase (NSE), chromogranins (A, B, C), synaptophysin (P38), 7B2, and HCG are nonspecific markers with special relevance for the diagnosis of NFNETs.

CgA and NSE are excellent markers for GEPET, whereas Ki 67 (higher than 2%) or MIB-1 is a malignancy predictor (Table V). CgA is probably more specific and NSE, more sensitive (83-100%).

CgA has a sensitivity of 60-100% in patients with metastatic disease, but lower than 50% in patients with local tumors (15).

Among FNEPTs and carcinoids insulin, glucagon, somatostatin, gastrin, VIP, PP, serotonin (and its metabolite 5-HIAA in urine), etc., are titrated by RIA.

This hormone panel using RIA is relevant not only for biochemical diagnosis but also for follow-up, for the monitoring of response to chemotherapy and surgery (14,15).

Measuring PTH, calcium, calcitonin, prolactin, etc., is also mandatory.

DIAGNOSIS AND IMAGING TECHNIQUES

Gut NETs (mainly carcinoids) are localized using radiography and endoscopy (Fig. 2), and may be staged by endoscopic ultrasonography (EUS), which provides information about the depth and extension of the tumor, and that in turn facilitate endoscopic tumorectomy or polypectomy (1-2-cm carcinoids in superficial layers with no muscularis propria infiltration or adenopathies). Metastatic disease and occult tumors should be excluded with octreoscan and PET.

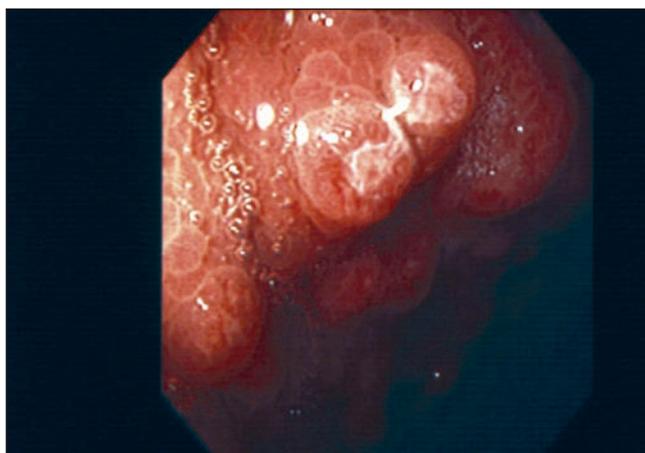


Fig. 2. Endoscopic image of gastric carcinoid tumors in the setting of MEN-1; although they can also be associated to atrophic gastritis or be sporadic.

Imagen endoscópica de carcinoides gástricos en el contexto de una NEM-1; aunque también pueden estar asociados a gastritis atrófica o ser esporádicos.

NEPTs are more difficult to localize; almost 20-30% of cases fail to be localized with imaging techniques (ultrasounds, HCT, gadolinium MRI, scintigraphy, octreoscan, etc.).

CT and MRI detect 30-94% of cases, and octreoscan detects 80-90% (except insulinoma: 50%), while EUS detects 79-100% (5).

Effectively, pancreatic EUS visualizes tumors as small as 3 mm with a sensitivity above 85% when located intrapancreatically in the head or body; even, in a study that analyzed a larger sample the sensibility was 93% in a paper published reporting a greater sample (19).

Literature reviews (20-22) suggest a high mean sensitivity at 88% with a specificity of 85%; hence, around 5-10% would still remain hidden preoperatively.

In our cumulative experience with 50 patients, 35 of whom had 34 tumors operated (14 in the pancreas, 20 in the gut, 15 carcinoids), EUS precision was 82.5%, with a sensitivity of 88% (94% for carcinoids, 90% for gut tumors, 86% for pancreatic tumors) and a PPV of 91%. Three tumors smaller than 10 mm, 4 smaller than 15 mm

(all insulinomas), and 1 cystic tumor 4 mm in size (2%), which was seen to be a functioning gastrinoma, were detected in the pancreas.

Outcomes over 10 years suggest a gradual increase in diagnostic accuracy and sensitivity as a result of experience (22).

EUS-FNAP was used for 10 cases (8 were operated upon) with an accuracy of 75%, sensitivity of and PPV of 83%, and specificity and NPV of 50%, since there was a false positive result (Table VI; Fig. 3.)

Table IV. Carcinoid syndrome in 10% of CTs (5)

Manifestations	Incidence	Mediators
Flushing	90%	Serotonin, histamine, subst. P, PGs
Secretory diarrhea	70%	5-HT, histamine, VIP, PGs, gastrin
Abdominal pain	40%	Obstruction, ischemia, fibrosis
Severe sweating	15%	Serotonin (5-HT), histamine
Facial telangiectasia	25%	Unknown
Heart disease	30% (right) 10% (left)	Substance P, serotonin
Pellagra, dermatitis	5%	Niacin deficiency
MEN	Rare	

When carcinoid syndrome develops in a pancreatic carcinoid tumor with liver metastasis, it is a carcinoid-like, atypical syndrome with chronic diarrhea. There is an increase in 5-HTP but not serotonin (5-HT) levels, the latter being elevated in typical CSs. Other mediators exist for carcinoid tumors: norepinephrine, neuro-peptide K, tachyins, bradykinin, neurotensin, etc.



Fig. 3. EUS-FNAP of NFNEPT (by courtesy of Gornals, MD). PAAF-USE de TNEPNF (cortesía del Dr. J. Gornals).

A localization and staging algorithm has been proposed based on the use of latest-generation helical CT and both radial and sectorial EUS when tissue samples are to be obtained with FNAP; accuracy and sensitivity are variously reported in the literature, but above 80% on average, and higher than 90% in the series with a greater use of FNAP (23).

In some cases (1.5-4%) (24,25), particularly very small NEPTs, most non-functioning masses (24-27), may show a cystic pattern, and EUS-FNAP may be successful in (26,27) in nearly 100% of cases.

Prevalence of NEPTS is estimated to be potentially higher at 9.5% (26), but our experience is similar (2%) to that reported in the reviewed literature (25).

Currently, the best strategy is likely the use of HCT plus optional EUS-FNAP. Octreoscan may be replaced by octotide PET in the future, with a sensitivity, specificity and accuracy above 90%.

These results may change in the future with the use of novel technologies such as USI, color EUS or EUS with Sonovue contrast (56), sonoelastography, intraductal ultrasonography using miniprbes, PET, etc.

THERAPEUTIC OPTIONS

1. *Surgery.* Classic or laparoscopic surgical therapy with total excision presently represents the only curative alternative after patient stabilization (fluids, diazoxide, PPIs, insulin... depending on tumor type).

Endoscopic polypectomy is indicated for digestive tract carcinoids smaller than 1-2 cm, located in superficial layers with no muscularis propria involvement, and in the absence of adenopathies (22).

2. *Somatostatin and somatostatin analogs (octreotide, lanreotide, pasireotide).* They inhibit hormone secretion. They may be administered via the subcutaneous or intramuscular route daily or every 7-14-30 days at doses oscillating between 100 and 1500 mcg/day in two to three subcutaneous injections. For intramuscular use 20-30 mg are administered every 7-14-28 days based on response – even 20 mg monthly. They do not regress tumors (3-14%) but do stabilize 36-70% of masses, and reduce clinical (> 50%) and biochemical (43%) parameters (28).

3. *Interferons.* Human leukocytic interferon and human recombinant interferon alfa-2B are administered subcutaneously, the latter at a dosis of 2 to 6 million IU/day for several weeks, for a tumor response of 11% and a biochemical response of 44% on average (29,30). According to a recent study with pegylated interferon alfa the disease would stabilize in 75% of cases (31) with symptom management.

4. *Chemotherapy.* With streptozotocine (1 g i.v./m²/day in 5-7-day courses every 6 weeks), streptozotocine plus 5-FU, or doxorubicin; this leads to remission in up to 60% of patients. Combined cisplatin and etoposide may be used for poorly-differentiated NETs.

Oral temozolomide and thalidomide are used in patients with advanced metastatic disease (32).

5. *Radiotherapy and other treatments.* Palliative radiotherapy with In111-DTPA octreotide for non-resectable tumors with a positive octreoscan test, with partial remission and tumor size stabilization in over 60% of cases.

NETs may release multiple growth factors, vascular endothelial growth factor, platelet-derived growth factor, insulin-like growth factor, fibroblast growth factor, transforming growth factor, and epidermal growth factor, as well as their respective receptors. New molecules are

used to target these factors and their receptors, including monoclonal antibodies, mTOR inhibitors, tyrosine kinase inhibitors such as sunitinib, with a response rate lower than 20% (5); a recent report (33) of 107 patients, however, 44% of carcinoids and 62% of NEPTs exhibited at least some tumor regression and estabilization.

6. *Combinations of the above.* For instance, somatostatin analogs plus interferon alfa (30) or chemotherapy.

7. *For hepatic metastases.* Chemoembolization, ethanolization, criosurgery, and radiofrequency ablation; ultimately liver transplantation may be considered for younger patients with liver metastases and excised primary NEPT (15).

PROGNOSIS AND SURVIVAL

The prognosis of carcinoids is very poor when carcinoid syndrome develops (10% of cases), as this is a manifestation of advanced disease (liver metastasis).

The prognosis of NEPTs depends on functioning status, MEN status, primary tumor size and site, and presence of metastatic disease (tumor extension) (14).

According to Massachussets General Hospital statistics (168 NEPTs) 76% were benign, and 26% were malignant with liver metastasis. Actuarial survival was 77 and 62% at 5 and 10 years (10).

In benign NEPTs 5-year survival was 92, vs. 50% for malignant NEPTs (11).

Today, the primary concern of specialists regarding ZES is the development of liver metastases, which represent the most significant factor for poor prognosis.

When operated on with curative intent, gastrinoma shows a 15-year survival rate of 98%, versus 74% for non-surgical patients (34). In all, 29% of non-operated patients developed liver metastases.

According to Princess Margaret Hospital statistics (193 NET in 10 years: 72% carcinoids and 21% NEPTs) 5-year survival was 58%; in the multivariate analysis, age, primary site, and surgery with curative intent were independent predictors of survival. When curative surgery was attempted, survival at 5 years increased to 86% (35).

According to Mayo Clinic statistics (1483 NETs over 27 years with a high percentage of non-functioning tumors: 91%) advanced status and age were predictive for poorer survival, and better results were obtained for functioning versus non-functioning growths (8).

Patients operated on for MEN-1 have similar survival at 7-10-15 years, but with high recurrence rates; only 4.5% are free from tumors at 10 years (36).

Survival for NET without liver metastasis was 95-90-83% at 5-10-15 years, respectively; even for malignancy, survival at 5 years may be up to 77-95% when aggressive treatment is attempted with primary tumor resection and adjuvant therapy, versus 36% at 5 years in other studies (4).

Several aspects are associated with poor prognosis: tumor size greater than 2 cm, presence of vascular or perineural invasion, pancreatic capsule infiltration, histological differentiation (poor differentiation), mitosis numbers, cell atypia, high Ki67 (higher than 30%), and presence of liver or lymphatic metastases.

In 70 patients operated upon for NEPT (23% insulinomas, 71% non-functioning, 53% malignant) actuarial survival at 5 years was 77%. Positive nodes, perineural invasion, and liver metastasis had no impact on survival, only lympho-vascular invasion had it (37).

German authors (38,39) having studied nearly 400 NETs, 70% with metastasis at diagnosis, believe that tumor size smaller than 2.5 cm, surgery, absence of metastasis and symptoms, and low CgA and Ki67 are best as survival markers.

The Swedish team (40) studied prognostic factors in 324 patients with NEPT, with survival rates at 5 and 10 years of 64 and 44%, respectively. In the univariate analysis, tumor stage, radical surgery, non-functioning status, high Ki67 and CgA, tumor size, and sporadic (non-familial) nature appeared as significant prognostic factors; in the multivariate analysis only stage, radical surgery, and Ki 67 > 2% remained so.

Italian authors (41) studied 180 cases of NFNEPT with survival at 5, 10, and 15 years of 67, 49, and 33%, respectively, and confirmed that metastasis, poor differentiation, Ki67, and weight loss are prognostic factors (Table V).

American authors (42) studied a registry with 35,825 cases, and concluded that in the multivariate analysis pre-

Table V. Prognostic factors

All GEPETs or NETs:	<ul style="list-style-type: none"> - Age - Tumor size (2.5 cm) and location - Radical surgery - Metastasis - CgA and Ki67 or MIB-1 (2%)
NEPT (20%):	<ul style="list-style-type: none"> - Tumor size (2 cm) and location - Unknown primary tumor - Metastasis - Curative surgery - MEN - NF - Other: angiogenesis markers, chromosomes and genes.
NFNEPT (+50%):	<ul style="list-style-type: none"> - Metastasis - Poor cellular differentiation - Ki67 - Weight loss
Carcinoids (70%):	<ul style="list-style-type: none"> - Size (1 cm), confined to mucosa-submucosa - Metastasis - CS (typical or atypical) - Other

Discussed in the text (under Prognosis). Parameters taken from WHO GEPT classification (48). Data summarized from the references (50).

Table VI. Experience: 1994-2009 (15 years)

<i>Gut NET:</i>		
Pseudo-ZES (2 cases)		
Duodenal gastrinoma (ZES)	1 case	
Gastric NF	1	
Carcinoids (none in pancreas)	24	
1 CS from unknown primary tumor		
Subtotal	26	
<i>FNEPT:</i>		
Gastrinoma (ZES)	3	(1 MEN-1)
Insulinoma	6	(1 MEN ?)
Glucagonoma	1	(HMS)
Somatostatinoma	1	
<i>NFNEPT:</i>		
	3	
Subtotal	14	
TOTAL:	40 cases	

40 cases; 35 received EUS and 10 received EUS-FNAP. Cumulative personal experience 118 (1-2) + 40 = 158 cases.

dictive factors included tumor differentiation, stage, primary tumor location, histological grade, sex, race, age, and year of diagnosis; they confirmed increased incidence, which changed from 1 per 100,000 in 1973 to 5.25 per 100,000 in 2004.

These data are consistent with incidences (1993-2004) in the USA and Norway, 4.44 *versus* 3.24 in Caucasian patients, and higher in Afroamerican subjects. Most frequent were always bronchopulmonary tumors (32%). Survival at 5 years for all NETs was 55% (43).

Regarding bronchopulmonary NET, most examples are little-functioning carcinoid tumors (-5%) with Cushing syndrome, acromegaly, and SIADH. Incidence in 2003 was 1.57 per 100,000, and on the rise. Survival at 5 years was 88% for typical carcinoid tumors with scarce growth (44).

GEPETs were previously considered to be more common than bronchopulmonary tumors, albeit a recent registry of 1,000 cases in Brazil showed 72% in the thorax, 20% GEPETs, and 3.6% in unknown places (45).

SUMMARY AND CONCLUSIONS

Neuroendocrine tumors (NETs) or gastro-entero-pancreatic endocrine tumors (GEPETs) may be carcinoids in 70% and pancreatic in 20% of cases.

Their incidence is higher than 5 cases per million population per year, and is currently increasing.

They may be sporadic or linked to genetic mutations.

They may be functioning (50%) or non-functioning; benign or malignant as a function of the presence of metastatic disease (50-60%).

Clinical suspicion should lead physicians to order a hormone panel with nonspecific markers such as CgA

and NSE, or specific markers including insulin, gastrin, VIP, serotonin -5-HIAA, etc.

Currently, the diagnostic algorithm for gut carcinoids includes endoscopy with biopsy, HCT, and octreoscan *vs.* PET.

For NEPT and MEN, the best strategy is seemingly HCT plus radial or sectorial EUS with optional FNAP (Fig. 3), followed by octreoscan *vs.* PET.

PET using ⁶⁸Ga-DOTA-Tyr3-octreotide has a sensitivity of 97%.

Following patient stabilization for inappropriate hormone secretion (fluids, diazoxide, PPIs, insulin, etc.), in the absence of metastasis surgery should be attempted with curative intent; when metastasis is present, adjuvant therapy should be added.

In advanced disease, treatment should be attempted with somatostatin analogs, interferons, both, or even chemotherapy or radiation therapy with octreotide when a positive octreoscan is obtained.

Prognosis and survival mainly depend on potential curative-intent surgery, the absence of advanced metastatic disease, and probably lymphovascular invasion (37).

Additional significant factors include primary pancreatic tumor size above 2.5 cm, high CgA and Ki67 (38-40), and metastasis, Ki67, and weight loss for NFNEPT (41).

For gut carcinoids (Fig. 4) smaller than 1 cm, endoscopic polypectomy is satisfactory and has replaced classic surgery for tumors not infiltrating the muscularis propria and with no metastatic disease (46). In such cases, and in appendicular carcinoids, 5-year survival rates are above 95%, while they decrease to 25 and 65% in the presence of liver or nodal metastases (47-49).

Despite recent advances in the diagnosis and treatment of NEPT (48,49), survival improvement remains unclear. In a recent review (51) no changes have been recorded

for survival rates during the past 30 years regarding all GEPETs (carcinoids and NEPTs) (52).

Recent papers advocate for the surgical resection of pancreatic tumors (53), but in patients with metastatic disease primary tumor resection is not beneficial for midgut-derived carcinoids (54).

Four cases of GEPET have been recently reported in patients with HIV infection (55).

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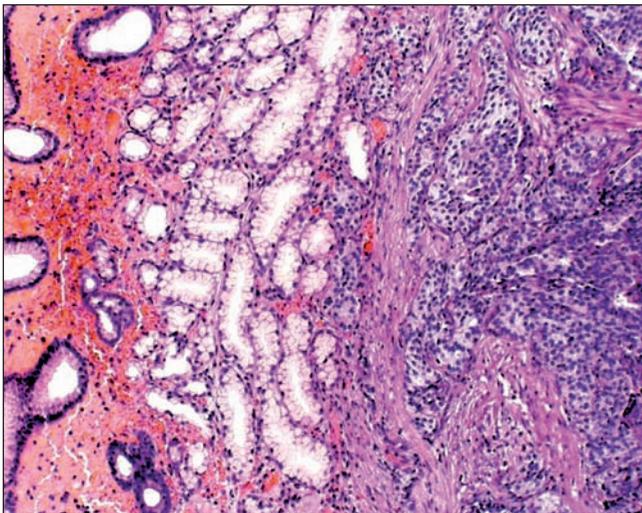


Fig. 4. Histopathology image of a carcinoid tumor.
Imagen anatomopatológica de un carcinoido.

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