Well differentiated neuroendrine tumors. Therapeutic approaches in gastric, appendicular and rectal carcinoids

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As predictors of response to therapy, cell proliferation and the proliferative fraction are good predictors, followed by differences in terms of size of the origin tumor such as stomach, appendix, colon and rectum.

The size and angioinvasion for the stomach, the size and meso invasion for the appendix, and the size and wall invasion in the case of the colon and rectum are major predictors (Table 1).

Table 1. *Selected Prognosticators for Endocrine Tumors-/Carcinomas in the Gastrointestinal Tract and Pancreas According to Site. (Predictors of Therapy Response).*

Stomach
Cell differentiation, gender, size, angioinvasion, proliferative fraction, clinicopathological subtype

Pancreas
Cell differentiation, proliferative fraction, distant metastases, abdominal pain, weight loss

Ileum
Gender, proliferative fraction, liver metastases

Appendix
Cell differentiation, proliferative fraction, size, meso-invasion

Colon and rectum
Cell differentiation, size, wall invasion, proliferative fraction

When discussing diagnosis modality -apart from MRIs, CT scans, PETs, CT scans + SSR- in terms of gastrointestinal mucosa in endocrine tumors of the colon and rectum, endoscopy and endoscopic ultrasound are also to be considered. And the future is for PET with Galium because it has mayor sensitivity for diagnosis and it costs is three times less than Octreoscan.

Endoscopic ultrasound in GEP NETs has the following advantages: It is useful in identifiying tumor location (fundus and gastric body); when it has a high frequency probe, it allows the diagnosis of single or multiple small subepithelial mass, and the diagnostic sensitivity reaches 80%. It is important for diagnosis, therapy and follow up (Table 2).

How many patients can be treated? If we look at the estimates, in a group including 100 patients, 34 of them having endocrine tumors (gastric and rectal carcinoids being the most frequents) can be treated. The best results for these patients can be obtained by surgery or endoscopy. Among poorly differenciated tumors surgery is less important and systemic treatment is more relevant.

Table 2. *Endoscopy ultrasound in GEP-NETs.*

EUS and GEP NETs

	Gastric Carcinoid (I –II)	Gastrinoma	NF PET
Location	Gastric body and fundus	Gastrinoma triangle and wall of duodenum	Intrapancreatic
EUS Device	High frequency probe	Linear EUS	Radial and Linear EUS
Endoscopic appearance	Single multiple small subepitelial mass	Solitary-multiple (MEN I) homogenous mass	Homogenous mass
Diagnostic Sensitivity *	>80 %	>80 %	>80 %

* + FNA

Gastric carcinoids

These tumors are divided into: type I , associated with atrophic gastritis; type II, associated with MEN I and type III, sporadic, not associated with any other diseases. GETs (type III tumors) are very rare tumors without predisposing factors for their development.

Dysplastic lesions in the gastric mucosa present the following general features: not endoscopically detectable, usually first diagnosed on histological examination, size ranges between 150-500 mm, they are detached in the mucosal depth, include moderately atypical endocrine cells with large nuclei, exhibit less immunohistochemical reactivity for granular markers, and spy lesions for occult multicentric ECL-carcinoid. Between dysplastic alterations and carcinoids the way is short. As for dysplastic lesions, the histological pattern shows:

enlarged micronodules, adenomatous micronodules, fused micronodules, microinfiltrative lesions, nodule(s) with newly formed stroma. The detection of dysplastic lesions should be performed by experienced and skilled pathologists since the difference between 499 µm and 500 µm may mean the difference between benign or malignant disease. (Figures 1 to 5).

Figure 1. *Enlarged Micronodules.*

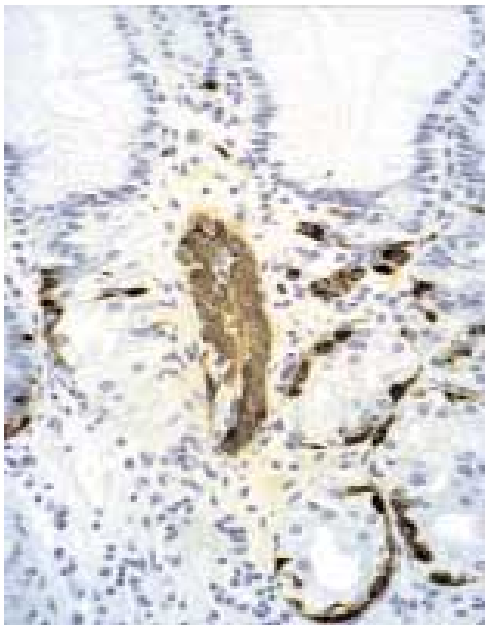


Figure 2. *Fused Micronodules.*

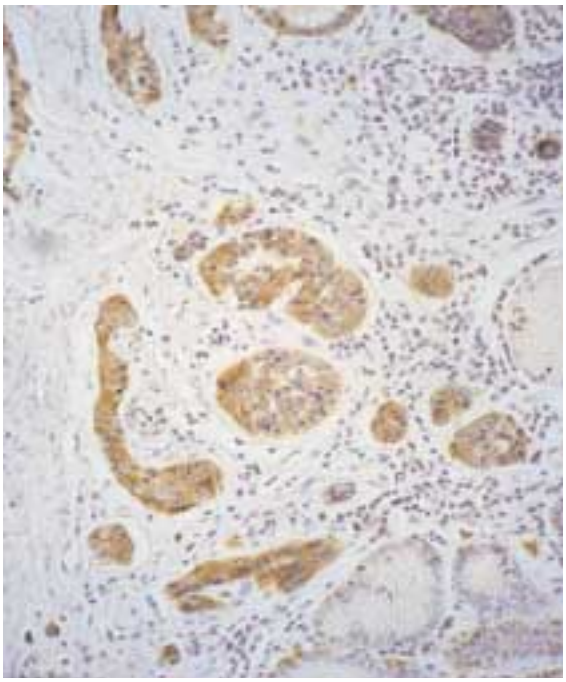


Figure 3. *Microinfiltrative Lesions.*

Figure 4. *Nodule with newly formed stroma.*

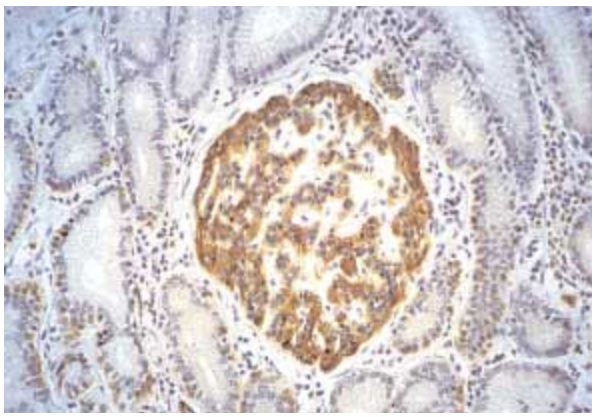
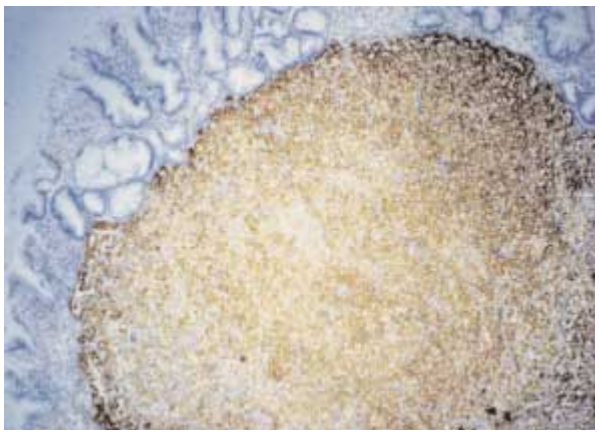


Figure 5. *Well Differenziated Endocrine Tumor (carcinoid).*



Dysplastic Lesions: Histological Patterns

Minimal consensus statement on symptoms and signs: They are not associated with clinical syndro-

me, they are non-functioning tumors. Carcinoids of gastric mucosa are detected incidentally. Symptoms are not specific, no carcinoid syndrome is observed; flushing and diarrhea are unusual. However, some specific symptoms like dyspepsia, mild pain and melena are present. Macroanemia is observed since it is associated with atrophic gastritis or bleeding.

As for the clinical spectrum of MEN 1 Syndrome, 30% of the patients have carcinoid. We have recently published a paper describing that all the patients with MEN 1 had dysplastic lesions and hyperplasia or enterochromaffin-like (ECL) cells. In MEN 1 carcinoids are present in 25% to 35% of patients.

A more detailed analysis of gastric carcinoids is needed: Type I is present in a large number of gastric carcinoids (70 to 80%) as compared to types II and III. Type 1 gastric carcinoids are associated with atrophic gastritis, which is an infection associated to *Helicobacter pylori*. More than 60% of the population in Western countries have *Helicobacter pylori* infection. This infection is a condition that predisposes to gastric cancer, and *Helicobacter pylori* has been found in all the atrophic gastritis that are present in autoimmune diseases. Plasma gastrin levels are increased in types I and II. Gastric pH is higher in type I. The risk of metastasis is very low in type I, and very high in type III. The tumor-related death is 0% for type I; < 10% for type II; 25-30% for the well-differentiated tumors and 75-87% for the poorly-differentiated tumors. The percentage of carcinoids is 2 to 3% in type I; 25 to 30% in type II (MEN 1 + ZEs); and 0 to 0,5 in type III. Carcinoids are rare, and almost not found in Zollinger Ellison Syndrome. The three types have elevated serum gastrin. At least 40% of the patients present carcinoids located in the intramucosa. Therefore, even if no evidence can be seen, a biopsy should be performed (Table 3).

Table 3. *Gastric carcinoids (Neuroendocrinology, 2004)*

	CAG Type I	MEN I + ZEs Type II	ZEs
Gastrin	↑↑	↑↑↑	↑↑↑
Intragastric pH	↑↑ (pH7)	↓↓ (pH 1-2)	↓↓ (1-2)
Endocrine cell hyperplasia	+++	++	++
Dysplasia	8-10 %	Yes	?
Carcinoids	2-3 %	25-30%	0–0.5 %

According to the algorithm, it is essential to perform a histological examination of the tumor and the gastric mucosa. Make maps of the right and left curves in order to rule out the presence of atrophic body gastritis. If there is atrophic body gastritis it is a type I carcinoid. Otherwise, you have to rule out the presence of MEN 1 syndrome. If there is MEN 1 syndrome, it is a type II carcinoid. Value the deep wall/ angioinvasion. If there is no MEN1 syndrome, then it is a type II carcinoid, and surgery is the option. Type I carcinoid is managed with endoscopic resection. As for Type II carcinoid, even in the presence of angioinvasion, endoscopic resection is the option.

Type I carcinoids should undergo endoscopic resection; type IIIs should be surgically managed.

According to the Minimal Consensus Statements on Follow-Up: gastroscopy should be performed every 2 years in patients with type 1 tumors, and yearly in the case of type 2 tumors.

The Minimal Consensus Statements on Endoscopic/ Surgical Treatment states that 10 mm-tumors should undergo surveillance. For larger tumors, local endoscopic ablation (following EUS) should be performed. Endoscopic mucosal resection (EMR) is recommended for lesions close to and above 1 cm but without invasion of the muscularis propia.

In the presence of deep gastric parietal wall invasion and positive margins following EMR, antrectomy and local resection is performed in type 1 ECLomas and antrectomy is effective in most patients and more radical surgery is required if lymph nodes are positive. These two lateststatements should be followed by “question marks”.

Actually, looking at all the papers published in the literature, no type I carcinoid has shown any invasion. Wall invasion has been observed only in Type III carcinoids in patients with *Helicobacter pylori* infection and atrophy.

Minimal Consensus Statements on Medical Therapy: Biotherapy is not currently recommended in patients with type 1 and 2 tumors except in patients with functioning tumors and in type 2 patients if indicated for the underlying tumor disease (i.e. other endocrine tumors).

Exceptions may be made in case of metastatic disease in reference centers. This is crucial. There is usually no place for chemotherapy in patients with

type 1 or type 2 tumors (with the exception of metastatic disease which is rare). Peptide receptor radionuclide therapy (PRRT) may be considered as a treatment option, although there are no data currently available to support its use in this setting, as part of a clinical trial in patients with distant metastases. Wher no other treatment options are available.

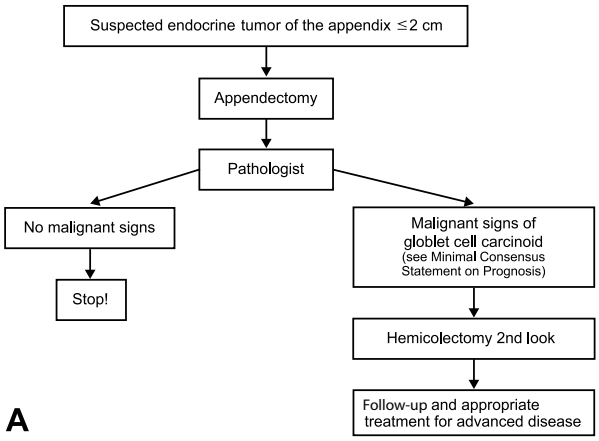
Appendiceal endocrine tumors

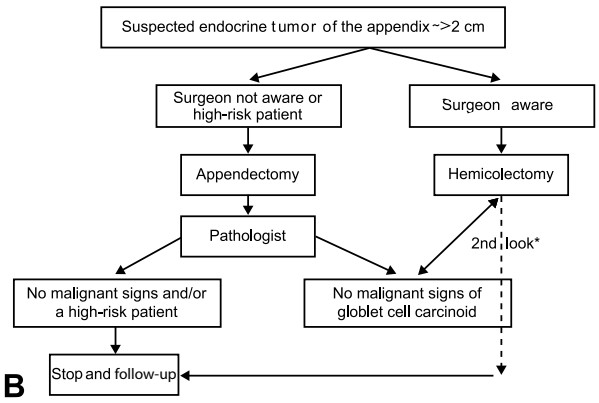
These NETs are the second most frequently occurring gastrointestinal endocrine tumors, with a relative frequency of 30 to 25%. If only malignant tumors are considered, 17% are located in appendix, 45% in small intestine, and 20% in rectum. A 35% to 85% of all appendiceal neoplasms are serendipitously diagnosed in 3 to 9 of 1,000 appendectomies. In a community hospital performing 100 appendectomies per year, at least one is detected.

Minimal Consensus Statement on Symptoms: appendiceal endocrine tumors are diagnosed incidentally during appendectomy, and association with a carcinoid syndrome is rare. They do only occur in tumors with widespread disease.

Minimal Consensus Statement on Prognosis: from the available data it can be deduced that an appendiceal endocrine tumor, at any location, a size < 2 cm, with invasion up to the subserosa or mesoappendiceal invasion up to 3 mm, poses no further risk after appendectomy. Size 1 to 2 cm deep mesoappendiceal invasion or margin invasion confer a relevant risk of recurrence and further surgical procedures are warranted (Table 4, A and B).

Table 4. *Suspected endocrine tumor of the appendix.*





Rectal carcinoids

They are diagnosed in relatively young patients (mean age at diagnosis: 56 years).

Rectal tumors are usually small, polypoid lesions located between 4 and 20 cm above the dentate line on the anterior or lateral rectal wall, and are mainly discovered incidentally on routine sigmoidoscopy. Since rectal carcinoids usually contain glucagon and glicentin instead of serotonin, so they rarely cause the carcinoid syndrome.

Small rectal carcinoids (those larger than 2 cm) rarely metastasize and endoscopic or other transanal excision is curative. Larger tumors carry a higher malignant potential with subsequent metastases to bone, lymph nodes and liver. Overall distant metastases occur in only 2.3%. The incidence of functioning tumors in the colon and rectum is extremely low.

Minimal Consensus Statement on diagnosis: Colonoscopy is the gold standard for detecting and characterizing colorectal polyps. CT colonography/MR imaging and 111 In-octreotide scanning is required for staging if residual or metastatic disease is suspected. EUS is important for assessing rectal carcinoids. Serum chromogranin A may be elevated. It is unusual for colorectal NETs to be associated with carcinoid syndrome.

The use of somatostatin analogues and interferon as anti-tumor agents should be in the context of a clinical trial. Chemotherapy is appropriate for poorly differentiated or high-grade NETs, but has little role in moderately- or well-differentiated colorectal NETs.

PRRT may be considered in patients with metastatic disease and positive nuclear medicine imaging.