ANNALS OF GASTROENTEROLOGY 2008, 21(2):88-97

Review

The current status in diagnosis of gastrointestinal carcinoid tumors

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SUMMARY

The carcinoid tumor, argentaffinoma, is a member of a very exclusive neoplastic family, known also in the past as neuroendocrine or amine precursor uptake and decarboxylation tumors. Carcinoids have been found to arise from almost every organ and system derived from the primitive endoderm, but most frequently originated from the gastrointestinal tract, accounting for approximately half of all gastrointestinal endocrine tumors. Between 75,5 and 90% of all gastrointestinal carcinoids are located in only three sites: the appendix, rectum and small intestine. Irrespectively to their location, carcinoids are capable of producing various peptides. These tumors may present at different disease stages with either hormonal or hormonal-related symptoms/syndromes, or without hormonal symptoms and may occur either sporadically or as a part of hereditary syndromes. Their clinical course is often indolent but can also be aggressive and resistant to treatment. This review provides a broad outline of progress that has been made in the elucidation of their clinical and laboratory diagnosis including recent advances in genetics, molecular biology, histopathology, biochemical markers, radiologic and scintigraphic imaging and endoscopy of gastrointestinal carcinoid tumors.

Key words: Carcinoid, neuroendocrine tumors, gastrointestinal carcinoid, somatostatin, octreoscan

BACKGROUND

The pathologic entity of carcinoid, or argentaffinoma, is a member of a very exclusive neoplastic family, known also in the past as neuroendocrine or amine precursor uptake and decarboxylation tumors and it has been found to arise from almost every organ and system derived from the gastrointestinal (GI) tract, accounting from approximately half of all GI endocrine tumors[1].

The carcinoid tumors of the GI tract have been attracting the attention of the medical community since their very first identification, at the end of the 19th century. The term "karzinoid" (carcinoma-like) was introduced in the medical vocabulary in 1907 by Oberndorfer, to describe an entity of tumors, which he believed to behave in a more indolent fashion than adenocarcinomas[2]. In 1914 Gosset and Masson stated that carcinoids should be considered as endocrine-related tumors and in 1963 Williams and Sandler proposed a classification according to their embryologic site of origin as foregut (respiratory tract, pancreas, biliary system, upper GI tract), midgut (small intestine, appendix, cecum, proximal colon) and hindgut carcinoids (distal colon, rectum).[3,4]

The incidence of carcinoid tumors varies with gender, age and race[5,6,7]. The overall incidence in the United States, Europe and Japan is estimated to be between 0.7 and 2 cases per 100,000 people, but in autopsies the rate tends to be much higher.[5-9]

This article provides a relevant update of the clinical and laboratory diagnosis of GI carcinoid tumors and briefly summarizes their main features.

GENETICS

The genetic substrate of carcinoid tumorgenesis is not yet fully understood. Several genetic syndromes including multiple endocrine neoplasia syndrome-type 1 (MEN 1) and neurofibromatosis-type 1 (NF1) may be associated with GI neuroendocrine tumors and a large number of he-

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reditary and familial mutations of p53, K-ras-2, MEN 1, bcl-2, C-raf-1, n-myc and c-jun, abnormal bcl-2: bax ratio and DNA ploidy have been correlated with prognostic factors of the tumors reported above.[10-16].

Aberrations in these genes, that in normal cells have an important role in tumor suppression, can lead to the development of several neoplasias, including carcinoid tumors.

p53: The p53 protein is encoded on chromosome 17. Although its wild type has a short half-life, the vast majority of mutant types present a longer half-life and for this reason are easily detectable, mainly in the carcinoid tumors of the lung.[17,18]

bcl-2: In one study, bcl-2 has been implicated as an active oncogene in the early phases of the carcinogenic process in gastric carcinoids.[19]

MEN 1: Less than 10% of patients with MEN1 syndrome have carcinoid tumors.[20] On the other hand, 44-78% of patients with spontaneous carcinoid tumors present loss of heterozygosity on chromosome 11 (11q13), where the MEN1 gene is localized.[20,21] Almost 30% of individuals with MEN1 develop gastric carcinoids and loss of heterozygosity at the 11q13 location occurs in 75% of MEN1 Zollinger-Ellison syndrome carcinoids and in 41% of MEN1 gastrinomas.[23] Loss of heterozygosity at several locations distal to 11q13 and also alterations in other chromosomes (4q, 4p, 5, 9p, 16q, 17q, 18q, 18p, 18q, 19q, 19p, 20q) have been implicated in the development of midgut carcinoid tumors[24,25,26,27]. Finally, alterations on chromosome 11 may play a major role in the development of foregut carcinoids.[27]

NF1: NF1 gene mutations were observed in a small number of patients with duodenal carcinoid tumors located in the ampula of Vater.[28-30]

MOLECULAR BIOLOGY

The activation of the insulin-like growth factor 1 (IGF1) receptor system (IGF1/IGF1R) is a critical event in the transformation and tumorgenicity processes of GI carcinoids. Two alternatively spliced IGF1R mRNA transcripts have been described to differ by only three nucleotides in the coding sequence. Examination of the relative expression of these isoforms demonstrated a significantly higher expression of both transcripts in GI carcinoid tumor cells.[31] Additionally, blockade of the IGF1 signaling via the induction of the raf-1/MEK1 pathway has been proposed as a possible therapeutic target in these malignancies of GI tract.[32]

Vascular endothelial growth factor (VEGF), transforming growth factor a and b (TGF-a, TGF-b), epidermal growth factor receptor (EGFR) and platelet-derived growth factor (PDGF) have been demonstrated also in GI carcinoids and in some cases in their metastases.[33-37]

Recent studies suggesting an overexpression of several proteins such as CDX2, NAP1L1, MAGE-D2, MTA1, TPH, VMAT1 and surviving, indicate these as potential markers for the diagnosis and differential diagnosis of these neoplasms.[38-40]

Finally, manipulation of Notch1 signal transduction pathway in human carcinoid cells may be useful for expanding the targets for therapeutic and palliative treatment of patients with carcinoids.[41]

PATHOLOGY-CLINICOPATHOLOGICAL STAGING

Because of the term "carcinoid" is no longer adequate to cover the entire morphologic and biologic spectrum of neoplasms of the disseminated neuroendocrine cell system, the WHO classification proposed for these tumors the general terms "neuroendocrine tumor" and "neuroendocrine carcinoma".[43] In this classification, distinction was made between well-differentiated neuroendocrine tumors (benign behavior or uncertain malignant potential), well-differentiated neuroendocrine carcinomas (low grade malignancy), and poorly differentiated (usually small cell) neuroendocrine carcinomas of high-grade malignancy. The term "malignant carcinoid" was used synonymously to term "well-differntiated neuroendocrine carcinoma", and to refine further the classification, a further subdivision utilizing localization and biology of the tumors was included to achieve a prognostic relevant classification.

Foregut neuroendocrine tumors: According to the ENETS (European Neuroendocrine Tumor Society) guidelines, gastric neuroendocrine tumors are categorized into well (the vast majority) or poorly differentiated tumors.[44,45]

Three subtypes of well differentiated gastric carcinoids, called also enterochromaffin-like (ECL)-cell carcinoids or ECLomas have been recognized (type I, II and III).

Midgut neuroendocrine tumors: According to the WHO indications, tumors of the duodenum and upper jejunum are classified together[46]. Well differentiated –carcinoids- are the majority. Most of them are mainly composed of gastrin-producing, somatostatin-producing or serotonin-producing cells. They may be either benign and of uncertain behaviour (WHO group 1), or low-grade malignant

(WHO group 2). Poorly differentiated carcinomas (WHO group 3) are rare and highly malignant.

Carcinoid tumors of the distal jejunum and ileum are mainly enterochromaffin cell tumors containing serotonin.

Clinicopathologically they are classified as:

1. Well-differentiated endocrine tumors (carcinoids)
2. Tumors of uncertain behaviour
3. Well-differentiated endocrine carcinomas (malignant carcinoids)
4. Poorly differentiated endocrine carcinomas
5. Mixed exocrine-endocrine carcinomas-moderate to high-grade malignants

On the other hand, endocrine tumors of the appendix are classified as:

1. Well-differentiated endocrine tumors (carcinoids)
2. Well-differentiated endocrine carcinomas (malignant carcinoids)
3. Mixed exocrine-endocrine carcinomas
4. Low-grade, malignant, goblet cell carcinoids

Hindgut nuroendocrine tumors: Based on WHO and ENETS guidelines, the clinicopathological staging and classification of hindgut carcinoids are as follows[44,46]:

1. Well-differentiated endocrine tumors (carcinoids)
2. Well-differentiated endocrine carcinomas (malignant carcinoids)
3. Poorly differentiated endocrine carcinomas (small cell carcinomas)

The TNM classification: Recently, a newer staging system was proposed by ENETS [TNM staging system of (neuro)endocrine tumors]. Based on the WHO classification the TNM classification attempts to close the gap between the newer advances and the need for a better prognostic assessment of NETs.[47,48]

CLINICAL DIAGNOSIS

Carcinoid tumors are slow-growing neoplasms, in many cases clinically silent for years, and often detected when metastases have been developed and the typical syndrome occurs (carcinoid syndrome)(Figure).

They usually present with obscure clinical manifestations and a large number of investigatory procedures are needed prior to establishing the diagnosis.

Although clinical diagnosis is based on symptoms, biochemical confirmation is necessary[49]. On the other hand, topographic localization of the primary lesion and meta-

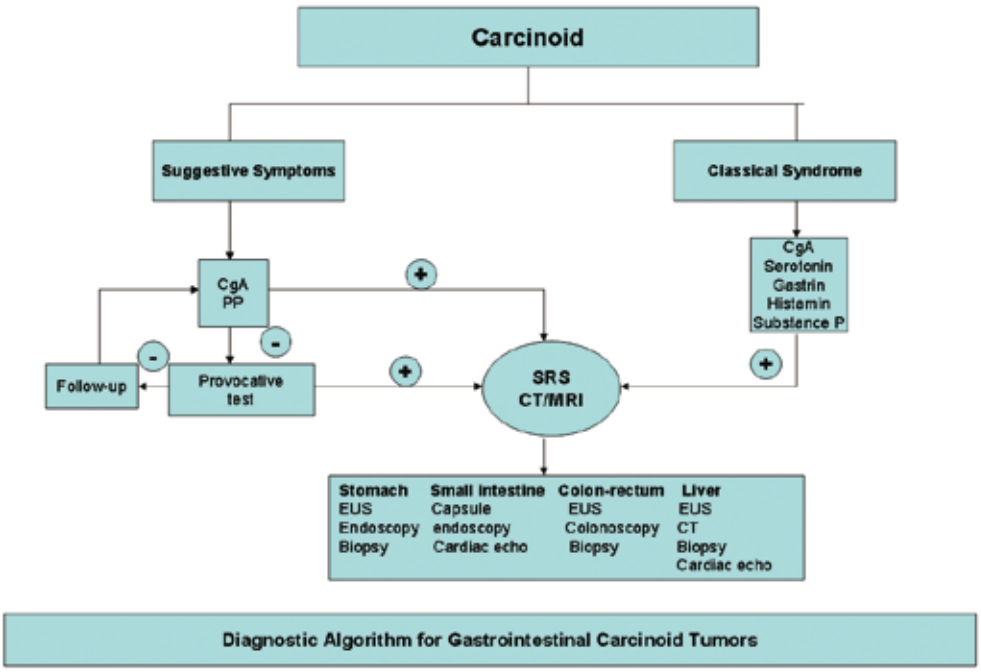

Figure 1: Diagnostic algorithm for gastrointestinal carcinoid tumors

static sites should be undertaken for determination of therapeutic strategy. Finally, care should be taken to consider issues special to carcinoids like multicentricity, associated neoplasms, peritoneal and cardiac manifestations, fibrosis and association with MEN syndrome or a familiar history[50].

BIOCHEMICAL MARKERS

Urinary 5-hydroxyindoleacetic acid (5-HIAA): Among the laboratory markers, the most widely available is urinary 5-HIAA (24h collection). Although certain serotonin-rich foods (tomato, kiwi, nuts, pineapple, eggplant, plum etc) and several drugs (acetaminophenol, coumarin, reserpine, nicotine, caffeine, melphalane, paracetamol, phenacetin, phenobarbital) can increase these levels and should be avoided during specimen collection, its specificity is reported to be almost 88%[51,52]. On the other hand, falsely low levels can be caused by ethanol, aspirin, MAO inhibitors and ranitidine.

5-HIAA serves as a sensitive tumor marker for diagnosis and follow-up in patients with carcinoid syndrome and should be estimated in two 24-hr urine collections.[44]

Three-quarters of patients with midgut carcinoid excrete urinary 5-HIAA as do approximately one third of patients with foregut carcinoids. Patients with hindgut carcinoid do not excrete this product. An assay for serum 5-HIAA has been described few years ago, which showed similar specificity, sensitivity and diagnostic potential to the urinary assay.[53]

Chromogranins (Cg's): The Cg's family is consistent by at least 3 different water-soluble acidic glycoproteins (CgA, CgB, CgC) stored in the granular vesicles of neuroendocrine and endocrine cells. Elevated plasma Cg's concentrations have become increasingly recognized as useful markers of GI neuroendocrine tumors including carcinoids[54,55].

Although a sensitivity of 100% was reported for CgA, 86% for CgB and only 5% for CgC, elevated CgA concentrations are not always specific for neuroendocrine tumors because several malignant (prostatic adenocarcinoma) and benign diseases (renal impairment, liver failure, atrophic gastritis, inflammatory bowel diseases etc) can be associated with elevated plasma CgA levels.[56-59]

CgA concentration is correlated in many cases with the tumor burden. Raised levels of CgA were noted in patients with midgut carcinoids and liver metastatic disease.[60]

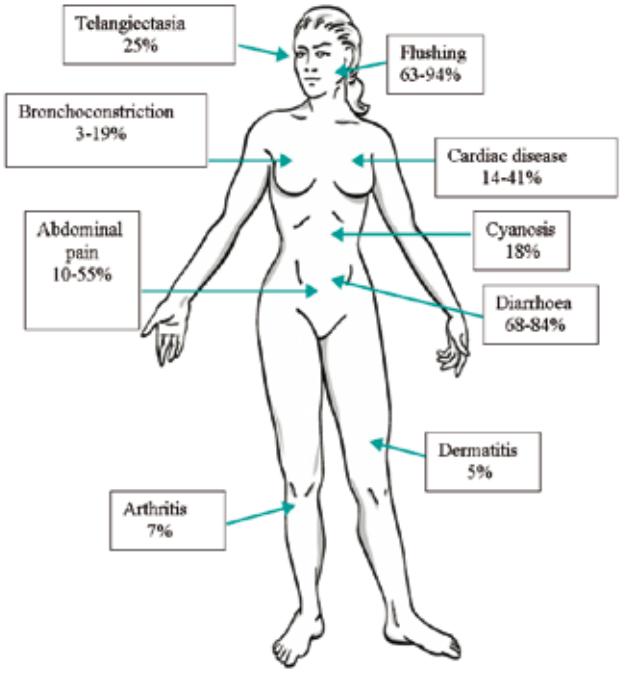

Figure 2: Carcinoid syndrome: Site and frequency of symptoms

For hindgut and foregut carcinoids, CgA appears to be an early and more sensitive marker than 5-HIAA.[56,61-63]

There are numerous assay kits for the CgA determination. Comparing three of these, Stridsberg et al reported satisfactory but not similar sensitivity and specificity.[64]

Recently, a new QRT-PCR methodology for the detection of CgA has been developed with a sensitivity 200-fold higher than that of the immunohistochemical methods.[65]

Other markers: Several other biochemical markers such as bradykinin, substance P, neurotensin, human chorionic gonadotropin (hCG), neuropeptide K and neuropeptide PP have been described but their specificity or predictive value was lower than that of CgA or 5-HIAA.[27]

Raised neurokinin A (NKA) levels have been identified in the vast majority of patients with midgut carcinoid tumors.[66]

Serum acid phosphatase levels may be raised in prostate-specific acid phosphatase-positive tumors[67]. β-hCG levels may also be increased.[67]

Biochemical niacin deficiency has been reported to be more prevalent in newly diagnosed patients with carcinoid syndrome than in controls.[68]

RADIOLOGRAPHIC AND NUCLEAR IMAGING METHODS

Radiology and nuclear imaging play an important role in the management and diagnosis of carcinoid tumors. On the other hand, extensive imaging is important for staging.

Octreoscan: Somatostatin receptor scintigraphy with the ^{111}In-labeled somatostatin analog (DTPA-d-Phe-10-[octreotide]) is a very sensitive method for the demonstration of the somatostatin receptor-positive tumors and their metastases.[69,70]

This analog shares the receptor-binding profile of octreotide, rendering it an ideal radiopharmaceutic for imaging of somatostatin 2 and 5 positive tumors.[71]

GI carcinoids express multiple somatostatin receptor subtypes but somatostatin receptor 2 predominance is generally found in the vast majority of these tumors[72]. Thus, with an overall sensitivity ranging between 80 and 90%, octreoscan is an effective method in detecting lesions not apparent by conventional radiologic imaging techniques[69,73].(Figure 3). Intraoperative application of the method is still under investigation. Although theoretically it appears to be superior to external somatostatin receptor scintigraphy, there are several practical and technical limitations to its use.[74] Apart from ^{111}In-pentetreotide, [^{111}In-DOTA^{o}]lanreotide can also be used.[75]

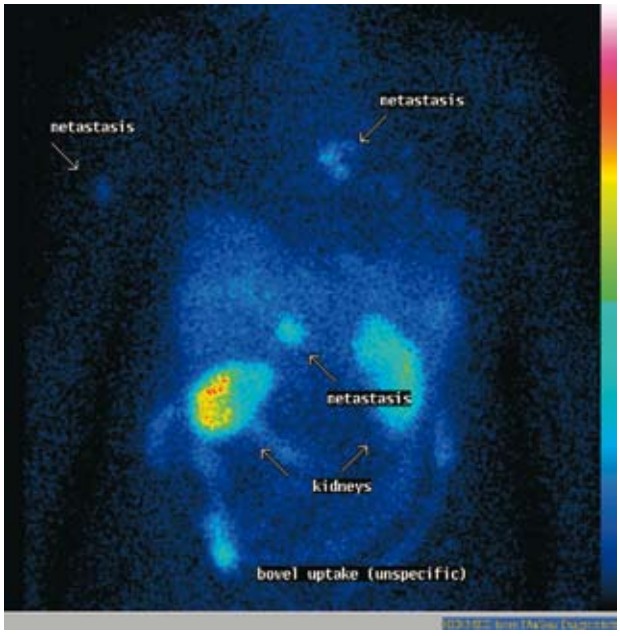

Figure 3: Octreoscan positive in a patient with midgut carcinoid

Single-photon emission computed tomography (SPECT) showed to improve accuracy of somatostatin receptor scintigraphy in abdominal carcinoid tumors. ^{111}In-pentetreotide SPECT appears to be more sensitive than planar scintigraphy, increasing the number of visualised tumor sites in patients with positive findings and for this reason plays an important role in the mapping of tumor spread and also in therapeutic decisions.[76-79] Thus, the use of SPECT images as recommended in: 1) Patients with specific functional clinical syndrome or with a known carcinoid tumor and normal planar images, 2) when planar images are abnormal only in primary tumor, 3) in order to confirm the absence of other metastases in patients with known liver metastases, 4) in order to enhance the detection of lesions with low receptor density and uncertain planar images and 5) in order to determine exactly the anatomic location of some lesions.[80]

Other nuclear scintigraphy techniques: Scanning with radiolabeled ^{123}I- and ^{131}I-meta-iodobenzylguanidine (MIBG) alone or in combination with computed tomography scans have been used[71,81]. With an overall sensitivity ranging between 55 and 70% and a specificity of 95%, ^{123}I-MIBG is less sensitive than octreoscan in detection of primary tumors and its role is limited in patients on long acting octreotide treatment in whom imaging may be compromised by analogue occupancy of tumor somatostatin receptors.[27,71,82]

Bone scintigraphy with ^{99m}TcMDP was used for identifying bone metastases from neuroendocrine tumors. Although the reported detection rates were similar with those of octreoscan, the combination of the two methods is not superior to ^{111}In-pentetreotide scintigraphy.[27,83]

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI): Contrast-enhanced CT scans or MRI of the upper and lower abdomen can be performed in patients with GI carcinoids to allow further localization of tumor deposits (Figure 4). Although CT and MRI provide important information on localization of metastatic sites from GI carcinoid tumors, their detection and sensitivity rates are lower than that of octreoscan (80% vs 89% and 80% vs 84% respectively).[84] Combination of the methods reported above with ^{111}In-pentetreotide scintigraphy enables higher accuracy of hepatic and lymph node metastases detection than each method alone in GI carcinoid tumor patients.[69,79]

Positron Emission Tomography (PET): Although there is limited experience with the use of PET scans in patients with GI neuroendocrine tumors several, mainly small, studies did not show superiority of the method as compared with octreoscan, CT or MRI.[84-86]

Table 1: Frequency of symptoms in gastrointestinal carcinoids by organ site (+: rare (<10%), ++: modest (11-50%), +++: frequent (>50%).

	Stomach	Small int.	Appendix	Colon	Rectum
Carcinoid Syndrome	+	++	+	+	+
Weight loss	+	+	+	+++	++
Vomiting	++	+	+	+	+
UGI bleeding	+	++	+	+	+
Rectal bleeding	+	+	+	++	++
Obstruction	+	+++	+	+	+
Constipation	+	+	+	+	+
Palpable mass	+	++	+	++	+
Pain/discomfort	++	++	++	+++	++
Asymptomatic	++	++	+++	+	++

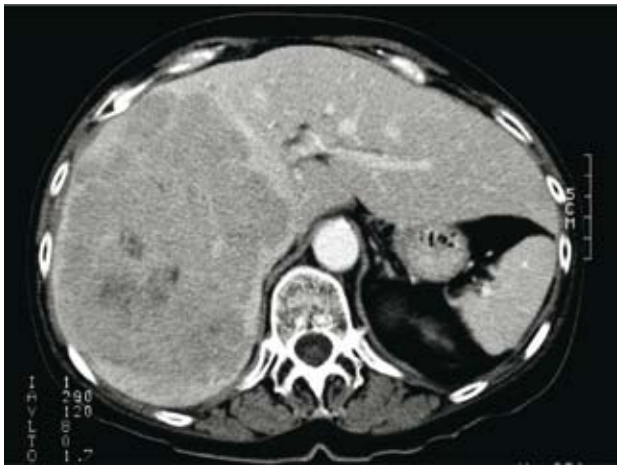

Figure 4. CT scan showing liver metastases in a patient with colon carcinoid

Recently, Orlefors et al reported detection rates of 95% and a superiority of the (11)C-5hydroxytryptophan PET as compared with CT scans and somatostatin receptor scintigraphy in patients with neuroendocrine tumors.[87]

[68Ga]-DOTATOC appears to be a promising PET tracer for imaging of neuroendocrine tumors and their metastases in a pilot study of four patients. In comparison to the [^{111}In]-DTPAOC-scan it seems to be superior, especially in detecting small tumors or tumors bearing only a low density of somatostatin receptors.[88]

Comparing several imaging diagnostic techniques (PET, CT, MRI, PET/CT, PET/MRI) in the assessment of the extent of metastatic sites in patients with GI carcinoid tumors, Seeman et al reported a superiority of PET scan in the detection of lymph node and osseous metastases and a superiority of MRI in the detection of liver metastases. On the other hand, PET/MRI combination was characterized as a promising diagnostic modality due to missing radiation exposure and the high soft tissue resolution.[89]

ENDOSCOPIC PROCEDURES

Gastroscopy and colonoscopy: Upper and lower GI endoscopy are, in the most cases, the initial diagnostic procedure for the detection of GI carcinoids. Gastroscopy with multiple biopsies from tumor and non-tumor tissue is essential for diagnosis and localization of the upper GI tract carcinoids to distinguish between the different types of gastric tumors and to exclude infection with Helicobacter pylori. Although carcinoid tumors rarely originate from the upper GI tract and are usually found accidentally after endoscopic examinations, their size may indicate a more severe disease and poor prognosis.[90]

In case of an unknown primary suspected carcinoid being present in the midgut, colonoscopy can identify a primary site in the distal ileum, at the ileocaecal valve or in the right-sided colon.

The vast majority of lesions in the rectum are also diagnosed endoscopically. Many lesions present as polyps with the diagnosis being made after histological studies. Full colonoscopic assessment is required to exclude concomitant colonic disease as part of staging and the possibility of synchronous carcinoma. The endoscopic features of rectal carcinoid tumors have been well described many years ago.[90] Central mucosal depression or ulceration suggests high metastatic potential.[91]

Enteroscopy: Because it is a time-consuming and uncomfortable procedure, not widely available and with low sensitivity (21-52%) its role in diagnosis of midgut carcinoid tumors is limited.[93]

Capsule endoscopy: The use of this method in detecting small intestine carcinoids is not yet well known.[94] Al-

though appears to be superior to CT and barium studies, his sensitivity and specificity rates, with the rapid Suspected Blood Identification System (SBIS), were reported low in a series that were included 7 patients with carcinoids. Thus, a complete review of the recording is still necessary.[95,96]

Endoscopic ultrasound (EUS): EUS is a highly sensitive method for detecting carcinoid tumors of the stomach and duodenum and is superior to conventional ultrasound, particularly in the detection of small lesions localized to the bowel wall because it can detect luminal lesions as small as 2-3 mm in size.[97,98]

It is also very useful in assessing rectal carcinoids preoperatively. EUS can accurately assess tumor size, depth of invasion and the presence or not of pararectal lymph node metastases. In conjunction with other investigative techniques, this provides important information with respect to choice of therapy.[99-101]

CONCLUSION

Gastrointestinal carcinoids are poorly understood malignancies, which, although slow growing compared with adenocarcinomas, can behave aggressively. An early and accurate diagnosis is often absent because symptoms and signs may be vague and non-specific. On the other hand, because each lesion is composed of its own distinct cells, each tumor behaves as a different biological entity. The need to define a plasma or genetic marker to predict or identify early lesions is paramount. For symptomatic patients with hormone secreting tumors there are a variety of generalised and specific biochemical tests. Measurement of circulating peptides and amines is also very helpful. The optimum imaging modality depends on whether it is to be used in detecting disease in a patient suspected of a NET or for assessing the extent of disease in a known case. Thus, for detecting the primary tumor, a multimodality approach is best and may include CT, MRI, somatostatin receptor scintigraphy, PET scan, EUS, endoscopy and capsule endoscopy, For assessing metastatic sites, somatostatin receptor scintigraphy is the most sensitive modality. When a primary site has been resected, somatostatin receptor scintigraphy may be indicated for follow up.

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