Diagnosis of carcinoid syndrome and tumor localization

AUTHOR: Jonathan R Strosberg, MD
SECTION EDITORS: Kenneth K Tanabe, MD, David C Whitcomb, MD, PhD
DEPUTY EDITOR: Sonali M Shah, MD

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Literature review current through: **Sep 2023.**
This topic last updated: **Apr 20, 2022.**

INTRODUCTION

The term "carcinoid" has been generally applied to well-differentiated neuroendocrine tumors (NETs) originating in the digestive tract, lungs, or rare primary sites, such as the kidneys or ovaries. In modern use, the term carcinoid is still used to refer to well-differentiated NETs arising in the lung (typical or atypical carcinoids), but within the gastrointestinal tract, the term carcinoid has fallen out of favor, and the World Health Organization (WHO) preference is for the term "NET." Regardless of site, the term "neuroendocrine carcinoma" is usually assigned to high-grade or poorly differentiated NETs. (See "Pathology, classification, and grading of neuroendocrine neoplasms arising in the digestive system", section on 'Pathology, tumor classification, and nomenclature'.)

NETs can present in several different ways:

- **As a result of carcinoid syndrome** – Chronic flushing and/or diarrhea are the typical manifestations of carcinoid syndrome, which is the result of secretion of serotonin and other vasoactive substances into the systemic circulation. Carcinoid syndrome is primarily associated with metastatic tumors originating in the midgut (distal small intestine and proximal colon). In contrast, hindgut (distal colorectal) and foregut (gastroduodenal, lung) NETs uncommonly produce carcinoid syndrome. (See "Clinical features of carcinoid syndrome" and "Lung neuroendocrine (carcinoid) tumors: Epidemiology, risk factors, classification, histology, diagnosis, and staging", section on 'Presenting signs and symptoms'.)

- **As a result of tumor growth** – Small bowel NETs may cause chronic/recurrent abdominal pain, occasionally leading to bowel obstruction. Metastatic tumors in the liver can cause right upper quadrant pain, hepatomegaly, and early satiety. (See "Clinical characteristics of well-differentiated neuroendocrine (carcinoid) tumors arising in the gastrointestinal and genitourinary tracts", section on 'Jejunoileal small bowel tumors' and "Metastatic well-differentiated gastroenteropancreatic neuroendocrine tumors: Presentation, prognosis, imaging, and biochemical monitoring", section on 'Clinical presentation'.)

- **As an incidental finding** – Many NETs are discovered during endoscopic or radiographic procedures planned for other purposes; this is especially true of NETs of the stomach and rectum.

This review will focus on the diagnosis of carcinoid syndrome and the localization/staging of well-differentiated NETs. Clinical and pathologic characteristics of NETs, treatment and prognosis of localized NETs, clinical manifestations and treatment of carcinoid syndrome, and treatment options for advanced metastatic gastrointestinal NETs are discussed separately:

- (See "Clinical characteristics of well-differentiated neuroendocrine (carcinoid) tumors arising in the gastrointestinal and genitourinary tracts".)
- (See "Pathology, classification, and grading of neuroendocrine neoplasms arising in the digestive system".)
- (See "Metastatic well-differentiated gastroenteropancreatic neuroendocrine tumors: Presentation, prognosis, imaging, and biochemical monitoring", section on 'Clinical presentation'.)
- (See "Staging, treatment, and post-treatment surveillance of non-metastatic, well-differentiated gastrointestinal tract neuroendocrine (carcinoid) tumors".)
- (See "Clinical features of carcinoid syndrome".)
- (See "Treatment of the carcinoid syndrome".)
- (See "Metastatic gastroenteropancreatic neuroendocrine tumors: Local options to control tumor growth and symptoms of hormone hypersecretion".)
- (See "Metastatic well-differentiated gastrointestinal neuroendocrine (carcinoid) tumors: Systemic therapy options to control tumor growth".)

BIOCHEMICAL TESTING FOR CARCINOID SYNDROME

Carcinoid syndrome is the result of secretion of serotonin and other vasoactive substances into the systemic circulation in the setting of a neuroendocrine tumor, most often a small bowel primary tumor with liver metastases. Hormone measurements in the blood and/or urine can

serve an important role in identifying and following patients with carcinoid syndrome. In general, nonhormonal peptide biomarkers (eg, chromogranin A [CgA]) markers are less useful. (See "Overview of tumor biomarkers in gastroenteropancreatic neuroendocrine tumors".)

The presence of carcinoid syndrome is usually considered when a patient has suggestive symptoms, such as otherwise unexplained chronic severe diarrhea and/or flushing. Clinical features of carcinoid syndrome other than flushing and diarrhea are presented elsewhere. (See "Clinical features of carcinoid syndrome".)

Differential diagnosis — Other conditions should be considered in the differential diagnosis, however:

- The differential diagnosis for flushing, for example, includes physiologic events, drugs, and a number of diseases other than carcinoid syndrome (table 1). (See "Approach to flushing in adults".)
- The differential diagnosis for diarrhea is broad. (See "Approach to the adult with chronic diarrhea in resource-abundant settings".)

In addition to the well-differentiated neuroendocrine tumors (NETs) of the gastrointestinal tract that cause carcinoid syndrome, other well-differentiated NETs arising in the pancreas may cause severe diarrhea, including gastrinomas and VIPomas. (See "Zollinger-Ellison syndrome (gastrinoma): Clinical manifestations and diagnosis" and "Management and prognosis of the Zollinger-Ellison syndrome (gastrinoma)" and "VIPoma: Clinical manifestations, diagnosis, and management".)

Assay of hormonal biomarkers can help in the differential diagnosis.

Hormonal markers

Blood serotonin concentration — We do not recommend measurement of blood serotonin levels as a standard diagnostic test for carcinoid syndrome. Various serotonin assays have been described in the literature, including whole blood serotonin, platelet-rich plasma serotonin, and platelet-poor plasma serotonin assays. However, the sensitivities and specificities of these assays are not well established. In one report, the mean fasting blood serotonin concentration in normal subjects ranged from 71 to 310 ng/mL (0.4 to 1.8 micromol/L). Ten patients with carcinoid syndrome had markedly elevated values, from 790 to 4500 ng/mL (4.5 to 25.5 micromol/L); of these, two had normal urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion [1]. Notably, false-positive serotonin tests may occur due to release of platelet serotonin in stored blood samples, as well as from the ingestion of tryptophan/serotonin-rich foods [2].

Urinary excretion of 5-HIAA — A preferred initial diagnostic test for carcinoid syndrome is to measure 24-hour urinary excretion of 5-HIAA, which is the end product of serotonin metabolism (figure 1). This test has a sensitivity of over 90 percent and a specificity of 90 percent for carcinoid syndrome [3]. Sensitivity is low in patients with NETs without carcinoid syndrome [4].

False-positive results may be induced by the ingestion of certain drugs and tryptophan/serotonin-rich foods (table 2). These foods should be avoided for three days prior to urine collection [5].

Measurement of urinary excretion of 5-HIAA is generally most useful in patients with primary midgut (jejunoileal, appendiceal, ascending colon) NETs, which produce the highest levels of serotonin. Foregut (gastroduodenal, bronchus) and hindgut (transverse, descending, and sigmoid colon, rectum, genitourinary) NETs only rarely secrete serotonin; they lack the enzyme dopa decarboxylase and cannot convert 5-hydroxytryptophan (5-HT) into serotonin and, therefore, into 5-HIAA (figure 1) [6]. These tumors may produce 5-HT (and histamine) instead of serotonin. However, there is no commercially available assay for urinary 5-HT.

The normal rate of 5-HIAA excretion ranges from 2 to 8 mg/day (10 to 42 micromol/day). Values of up to 30 mg/day (157 micromol/day) may be found in patients with malabsorption syndromes, such as celiac and Whipple's disease, as well as after the ingestion of large amounts of tryptophan- or serotonin-rich foods (table 2). Although many patients with carcinoid syndrome have similar modest elevations, some have values for urinary 5-HIAA excretion above 100 mg/day (523 micromol/day). In one study, for example, urinary 5-HIAA excretion in patients with carcinoid syndrome ranged from 99 to 2070 mg/day (518 to 10,826 micromol/day) [3].

Plasma 5-HIAA concentration — Plasma 5-HIAA measurement is a reasonable option, particularly for patients who have difficultly providing 24-hour urine specimens, although published experience with this assay is confined to a small number of institutions, and this test has yet to be validated in large clinical series.

Plasma 5-HIAA levels can be obtained from several laboratories, and reportedly correlate closely with urine 5-HIAA [7-9]. In one study of 115 NET patients, levels of fasting plasma 5-HIAA correlated very closely with levels of urine 5-HIAA ($p < 0.0001$) [8].

Gastrin and VIP — As noted above, some functional pancreatic neuroendocrine tumors (notably, gastrinomas and VIPomas) can be associated with severe diarrhea. In such cases, assays to 5-HIAA may be negative, but serum levels of gastrin and vasointestinal polypeptide (VIP) may be elevated, and aid in the differential diagnosis. (See "Overview of tumor biomarkers in gastroenteropancreatic neuroendocrine tumors", section on 'Hormones associated with pancreatic NETs'.)

Nonhormonal markers

Chromogranin concentration — Due to its relatively low specificity, we do not recommend the use of CgA as a screening test for the diagnosis of a NET or carcinoid syndrome. CgA may be an appropriate tumor biomarker for patients with an established diagnosis of advanced NET in order to assess disease progression, response to therapy, or, in some cases, recurrence after surgical resection. (See "Overview of tumor biomarkers in gastroenteropancreatic neuroendocrine tumors", section on 'Chromogranin A (CgA)'.)

Chromogranins (designated as chromogranin A [CgA], chromogranin B [CgB], and chromogranin C [CgC]) are proteins that are stored and released with peptides and amines in a variety of neuroendocrine tissues. Well-differentiated NETs, including carcinoids, are associated with elevated blood concentrations of chromogranins, which increase with larger tumor burden [5,10-12]. CgB and CgC are less sensitive indicators of NETs as compared with CgA [13].

Despite a high volume of published studies evaluating multiple circulating nonhormonal tumor markers like CgA in NETs, consensus-based guidelines have increasingly de-emphasized their role in clinical care for the following reasons:

- Levels of CgA secretion vary on a day-by-day basis in healthy subjects and those with NETs.
- Food intake also increases CgA levels [14,15]. False-positive elevations of CgA can be present in a number of other conditions, including atrophic gastritis (table 3). They are especially common in patients who are taking a proton pump inhibitor [16-18]. As a result, CgA is a relatively nonspecific marker for NETs [4,5,19].
- A recognized international standard for CgA assay is not available, and multiple CgA tests exist that use different assays, have widely divergent normal thresholds, and varying degrees of accuracy [20].

Sensitivity is limited for localized disease. Test performance is better with advanced disease and varies according to disease burden, and the specific cutoff value [11,21]. In general, serial measurements of CgA and/or other nonhormonal tumor markers are most useful in patients with metastatic NETs and highly elevated levels of the marker, which are more likely to be true-positives than false-positives. In such patients, serial assay of CgA levels may be a reasonable indicator of disease activity and response to antitumor therapy. Whenever we do measure tumor marker levels, we usually obtain them in conjunction with radiographic imaging, typically every 6 to 12 months. (See "Overview of tumor biomarkers in gastroenteropancreatic neuroendocrine tumors", section on 'Chromogranin A (CgA)' and "Metastatic well-differentiated

gastroenteropancreatic neuroendocrine tumors: Presentation, prognosis, imaging, and biochemical monitoring", section on 'Chromogranin A'.)

TUMOR LOCALIZATION AND STAGING

Tumors originating in intestinal tract — Carcinoid syndrome is primarily associated with metastatic neuroendocrine tumors (NETs) that originate in the small intestine or proximal colon. Vasoactive peptides that are produced by localized intestinal NETs are inactivated in the portal circulation and, thus, do not result in carcinoid syndrome. The liver is the most common distant metastatic site. Imaging studies should, therefore, focus on the abdomen and pelvis. Computed tomography (CT), magnetic resonance imaging (MRI), and diagnostic imaging using radiolabeled somatostatin analogs (SSAs; indium-111 pentetreotide [111-In pentetreotide; OctreoScan] and gallium Ga-68 DOTATATE [68-Ga DOTATATE]) are the primary imaging modalities used to identify NETs.

Computed tomography — CT scans are noninvasive and readily available. Multiphasic contrast-enhanced CT is recommended for evaluation of all patients with NETs, with the exception of tumors with a very low probability of spread, such as most type 1 and 2 gastric NETs or small (<1 to 2 cm) superficial (T1) rectal NETs [22,23]. (See "Staging, treatment, and post-treatment surveillance of non-metastatic, well-differentiated gastrointestinal tract neuroendocrine (carcinoid) tumors", section on 'Staging and treatment of localized tumors'.)

Most NET liver metastases are highly vascular, but approximately 6 to 20 percent are hypovascular [24]. Hypervascular metastases may appear isodense with the liver on a noncontrasted study. Following the injection of intravenous contrast, most NETs enhance with iodinated contrast during the early arterial phase (approximately 20 seconds after contrast injection), with washout during the portal venous imaging phase (approximately 70 seconds after contrast injection) [24,25]. Arterial phase and portal venous phase sequences maximize the conspicuity of liver metastases compared with the surrounding normal liver parenchyma (image 1).

The ability of CT to localize the site of the primary tumor in patients with carcinoid syndrome is variable:

- NETs originating in the jejunum and ileum are often difficult to identify on CT because of their small size. However, multiphasic helical CT performed with neutral oral contrast and multiplanar reformations can improve detection [24]. Arterial phase imaging can aid in detection of these early enhancing lesions. Small intestinal NETs often produce mesenteric

masses with dense desmoplastic fibrosis, either due to direct extension of primary tumors into the mesentery or due to mesenteric lymph node metastases (image 2). The classic finding on CT is a mass-like process with soft tissue "spokes" radiating into the mesenteric fat toward the small bowel, often causing retraction of the bowel with angulation and tethering. The central mass may or may not be calcified. The differential diagnosis includes sclerosing mesenteritis. (See "Staging, treatment, and post-treatment surveillance of non-metastatic, well-differentiated gastrointestinal tract neuroendocrine (carcinoid) tumors", section on 'Small intestine'.)

- Appendiceal NETs may not be seen on CT because of their small size [24]. The scan may only show features of appendicitis, such as diffuse thickening of the appendix or periappendiceal fat stranding. A larger tumor may present as a soft tissue mass in the appendix, with or without calcification. (See "Well-differentiated neuroendocrine tumors of the appendix", section on 'Staging and prognosis'.)

- Colonic NETs tend to be large (>2 cm) and more frequently involve the cecum and ascending colon. CT cannot differentiate a colonic NET from the more common adenocarcinoma since both present as circumferential thickening or polypoid masses and may have adjacent lymphadenopathy [24]. (See "Staging, treatment, and post-treatment surveillance of non-metastatic, well-differentiated gastrointestinal tract neuroendocrine (carcinoid) tumors", section on 'Colon'.)

Magnetic resonance imaging — MRI may represent the most sensitive method for detection of liver metastases. In one study of 64 patients with metastatic gastrointestinal NETs, multiphasic MRI detected more hepatic lesions than either CT or 111-In pentetreotide [26]. As a result of this greater sensitivity for liver metastases, some clinicians prefer MRI over CT for assessing the status of the liver in patients with NETs [27]. This subject is discussed in detail elsewhere. (See "Metastatic well-differentiated gastroenteropancreatic neuroendocrine tumors: Presentation, prognosis, imaging, and biochemical monitoring", section on 'Cross-sectional imaging'.)

However, even MRI can significantly underestimate the total tumor burden, especially when lesions are small. In a study comparing preoperative imaging with thin-section pathology mapping, the accuracy for detecting liver metastases was only 49 percent for MRI [28].

As with CT scans, early arterial phase imaging following the injection of contrast is critical for the detection of small hypervascular liver metastases. In a study of 37 patients with liver metastases from gastroenteropancreatic NETs, the most sensitive sequences for detection of liver metastases were hepatic arterial phase and fast spin-echo T2-weighed images [29]. In

another study comparing two MRI contrast agents, the delayed hepatobiliary phase using gadoxetate (Eovist) contrast provided the highest contrast-to-noise ratio as well as the highest levels of interobserver agreement on tumor diameter [30].

Somatostatin receptor-based imaging — Most well-differentiated NETs express high levels of somatostatin receptors (SSTRs) and can therefore be imaged with radiolabeled SSAs. These scans allow for whole body imaging. They also provide information on SSTR expression, which has important therapeutic implications regarding use of cold and radiolabeled SSAs. The first imaging technique to visualize SSTR-expressing tumors used 111-In pentetreotide to produce a scintigraphic image (OctreoScan). The accuracy of 111-In pentetreotide improved with the addition of single-photon emission CT (SPECT) to planar imaging (image 3) [31,32]. More recently, several positron emission tomography (PET) tracers for SSTR imaging have emerged (such as 68-Ga DOTATATE and 68-Ga DOTATOC), which in combination with CT, improve the detection and staging of NETs [33]. These novel PET modalities offer higher spatial resolution than conventional 111-In pentetreotide scanning and are associated with improved sensitivity for detection of small lesions, including occult primary tumors (image 4). In our view (and that of others [34]), 68-Ga DOTATATE or 68-Ga DOTATOC PET/CT, where available, is preferred over conventional 111-In pentetreotide scanning for tumor localization. This subject is discussed in detail elsewhere. (See "Neuroendocrine neoplasms of unknown primary site", section on 'Initial workup' and "Diagnosis and staging of small bowel neoplasms", section on 'Somatostatin receptor-based imaging'.)

Of note, poorly differentiated neuroendocrine carcinomas generally express fewer SSTRs and are not routinely evaluated with SSTR imaging [35].

Endoscopy — Upper and lower endoscopy (with attention to the terminal ileum) should be performed for the evaluation of metastatic NET if the primary site cannot be established through imaging studies. Other options include CT enterography. Although video capsule endoscopy has been used to detect the primary site in metastatic NETs, we do not recommend this study given several reports of obstruction following ingestion of the video capsule [36].

Lung neuroendocrine tumors — Uncommonly, lung NETs can present with carcinoid syndrome, even in the absence of hepatic metastases. As with intestinal primaries, cross-sectional imaging and diagnostic imaging with radiolabeled SSAs can be used to localize well-differentiated lung NETs (bronchial carcinoids). These tumors tend to be centrally located endobronchial lesions; however, approximately 20 percent arise peripherally and present as a well-circumscribed solitary pulmonary nodule (image 5). (See "Lung neuroendocrine (carcinoid) tumors: Epidemiology, risk factors, classification, histology, diagnosis, and staging", section on 'Clinical syndromes related to peptide production'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Well-differentiated gastroenteropancreatic neuroendocrine tumors".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Carcinoid syndrome (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Differential diagnosis**
  - The presence of carcinoid syndrome due to a neuroendocrine tumor involving the gastrointestinal tract may be suspected when a patient has otherwise unexplained diarrhea or flushing.
  - However, other diagnoses must be considered. The differential diagnosis of flushing, for example, includes physiologic events, drugs, and a number of diseases other than carcinoid syndrome (table 1). Moreover, other NET types arising in the pancreas (eg, VIPomas) can cause severe chronic diarrhea. (See 'Differential diagnosis' above.)
- **Approach to biochemical testing**

- **Urinary 5-HIAA** – The most useful initial diagnostic test for carcinoid syndrome is to measure 24-hour urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA), which is the end product of serotonin metabolism (figure 1). Depending on the cutoff value used, this test has a high sensitivity and high specificity for carcinoid syndrome but requires strict avoidance of foods containing serotonin and tryptophan as well as certain drugs for three days prior to the urine collection (table 2). (See 'Urinary excretion of 5-HIAA' above.)

  Measurement of urinary 5-HIAA excretion is generally not useful in foregut (gastroduodenal, lung) NETs, which often lack aromatic amino acid decarboxylase. In this setting, we would pursue imaging studies to search for a NET.

- **Serum chromogranin A** – Due to its relatively low specificity, we do not recommend the use of serum chromogranin A (CgA) as a screening test for the diagnosis of carcinoid syndrome. (See 'Chromogranin concentration' above.)

- **Tumor localization**

  - Once the biochemical diagnosis of carcinoid syndrome is confirmed, usually by an elevated 24-hour excretion of 5-HIAA, the tumor must be localized. (See 'Tumor localization and staging' above.)

  - Two techniques, standard cross-sectional imaging and somatostatin receptor-based imaging, have a complementary role in tumor localization:

    - For the diagnostic workup of carcinoid syndrome, we generally perform helical, contrast-enhanced, triple-phase CT scans of the abdomen and pelvis. (See 'Computed tomography' above.)

      Contrast-enhanced MRI of the abdomen and pelvis is an acceptable alternative and is preferred by some clinicians because of its greater sensitivity for liver metastases. (See 'Magnetic resonance imaging' above.)

    - Most well-differentiated NETs express high levels of somatostatin receptors (SSTRs) and can therefore be imaged with radiolabeled somatostatin analogs which can assist in identifying an otherwise occult primary site. Where available, functional imaging with gallium Ga-68 DOTATATE positron emission tomography (PET)/CT is preferred over indium-111 pentetreotide (OctreoScan) due to its greater sensitivity. (See 'Somatostatin receptor-based imaging' above.)

Poorly differentiated neuroendocrine carcinomas generally express fewer SSTRs and are not routinely evaluated with SSTR imaging.

- Upper and lower endoscopy (with attention to the terminal ileum) should be performed for the evaluation of metastatic NET if the primary site cannot be established through imaging studies. (See 'Endoscopy' above.)

ACKNOWLEDGMENT

The UpToDate editorial staff acknowledges Stephen Goldfinger, MD, who contributed to an earlier version of this topic review.

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Topic 2622 Version 38.0

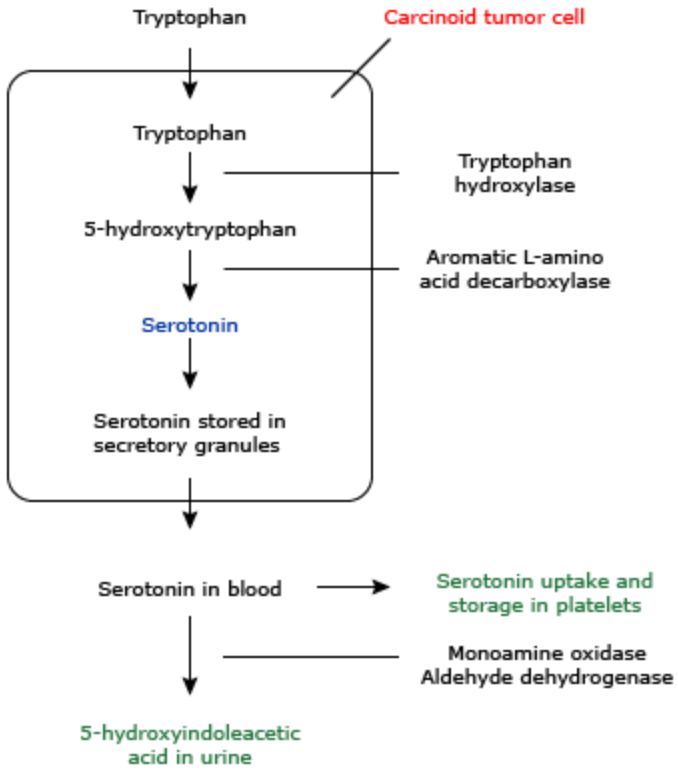
GRAPHICS

Causes of flushing

Type	Causes
Physiologic	Menopause
	Hot drinks
	Emotional distress
	Anaphylaxis
Drugs	Alcohol
	Alcohol plus chlorpromazine or disulfuram
	Diltiazem
	Amyl nitrate
	Nicotinic acid (niacin)
	Levodopa
	Bromocriptine
Diseases	Carcinoid syndrome
	Systemic mastocytosis
	Basophilic chronic granulocytic leukemia
	VIPoma
	Pheochromocytoma
	Medullary carcinoma of the thyroid
	Renal cell carcinoma
	Diencephalic seizures
	Postural Orthostatic Tachycardia Syndrome (POTS)

Graphic 78237 Version 3.0

Tryptophan and serotonin metabolism



Pathways of tryptophan and serotonin metabolism in the carcinoid tumor cell. Patients with the carcinoid syndrome often have increased levels of 5-hydroxyindoleacetic acid (5-HIAA) excretion in the urine and serotonin in the blood; urinary serotonin excretion is either normal or slightly increased.

Graphic 51368 Version 4.0

Substances that interfere with determination of urinary 5-HIAA

Falsely high values
Tryptophan-rich foods: avocados, pineapples, bananas, kiwi fruit, plums, eggplants, walnuts, hickory nuts, pecans, tomatoes, plantains, butternut squash
Drugs: acetaminophen, coumaric acid, guaifenesin, mephenesin, phenobarbital, reserpine, acetanilid, ephedrine, methamphetamine, nicotine, phentolamine, phenmetrazine, caffeine, fluorouracil, melphalan, methocarbamol, phenacetin, mesalamine
Falsely low values
Drugs: corticotrophin, ethanol, imipramine, levodopa, MAO inhibitors, phenothiazines, aspirin, isoniazid, gentisic acid, methenamine, streptozotocin, heparin, methyldopa

5-HIAA: 5-hydroxyindoleacetic acid; MAO: monoamine oxidase.

Reference:

1. *Corcuff J, Chardon L, El Hajji Ridah I, Brossaud J. Urinary sampling for 5HIAA and metanephrines determination: revisiting the recommendations. Endocr Connect 2017; 6:R87.*

Graphic 79968 Version 7.0

Conditions associated with elevated chromogranin A

Gastroenteropancreatic NETs
Gastrointestinal tract (carcinoid tumors)
Pancreatic NETs (islet cell tumors*)
Endocrine disease
Hyperparathyroidism
Hyperthyroidism
Pheochromocytoma
Pituitary tumors
Medullary thyroid carcinoma
Gastrointestinal disorders
Chronic atrophic gastritis
Chronic hepatitis
Colon cancer
Hepatocellular carcinoma
Inflammatory bowel disease
Irritable bowel syndrome
Liver cirrhosis
Pancreatic adenocarcinoma
Pancreatitis
Cardiovascular disease
Acute coronary syndrome
Arterial hypertension
Cardiac insufficiency/failure
Essential hypertension
Giant cell arteritis
Drugs
Proton pump inhibitors
Histamine-2 receptor antagonists
Inflammatory disease

Airway obstruction in smokers
Chronic bronchitis
Systemic rheumatoid arthritis
Systemic inflammatory response syndrome
Renal disorders
Renal insufficiency/failure
Non-gastrointestinal cancers
Breast cancer
Ovarian cancer
Prostate cancer¶
Small cell lung cancer
Neuroblastoma

NETs: neuroendocrine tumors.

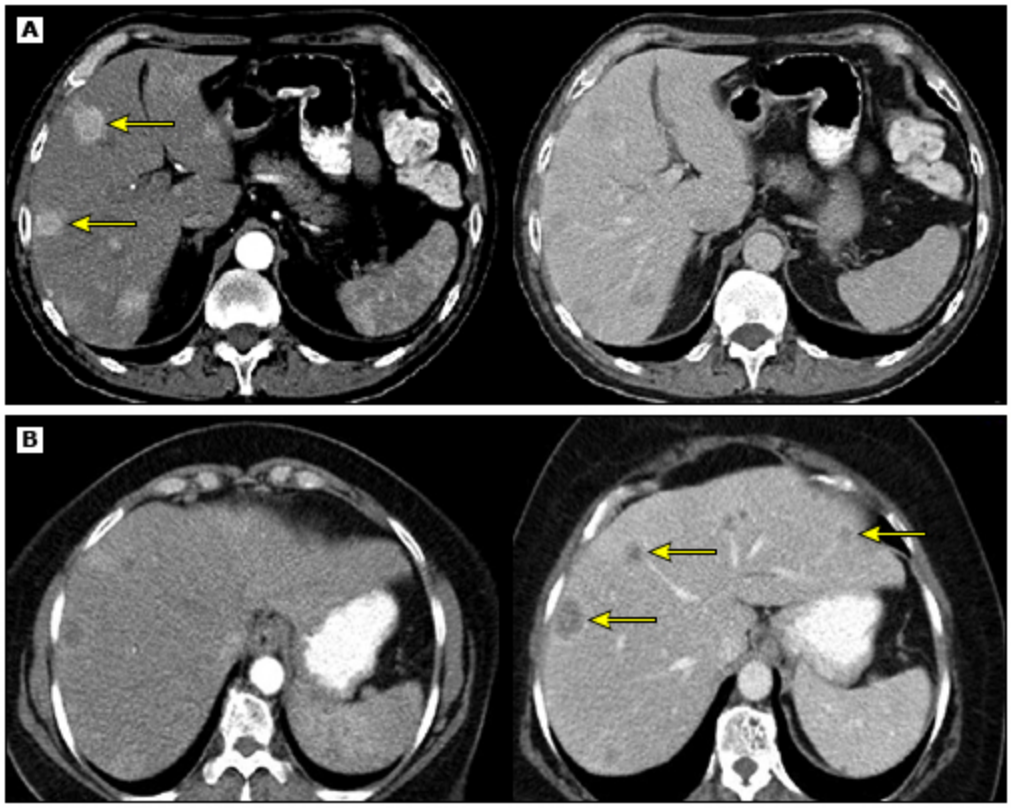
* eg, gastrinomas, VIPomas, somatostatinomas, glucagonomas, nonfunctioning pancreatic NETs.

¶ Even with a normal prostate-specific antigen (PSA) level.

Adapted from: Modlin IM, Gustafsson BI, Moss SF, et al. Chromogranin A--biological function and clinical utility in neuro endocrine tumor disease. Ann Surg Oncol 2010; 17:2427.

Graphic 73287 Version 7.0

CT of neuroendocrine tumor liver metastases

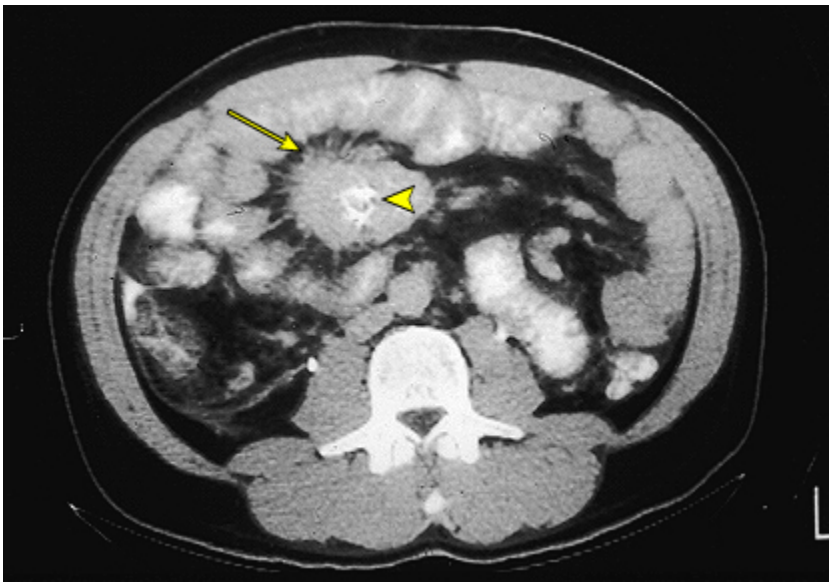


In patient A (top two images), the hypervascular liver metastases are more clearly observed on the arterial phase (left) compared to the portal venous phase (right); whereas in patient B (lower two images), the liver metastases are not as hypervascular and more clearly delineated on the portal venous phase (right) compared to the arterial phase (left).

CT: computed tomography.

Graphic 52935 Version 3.0

Radiographic features associated with small bowel neuroendocrine tumors

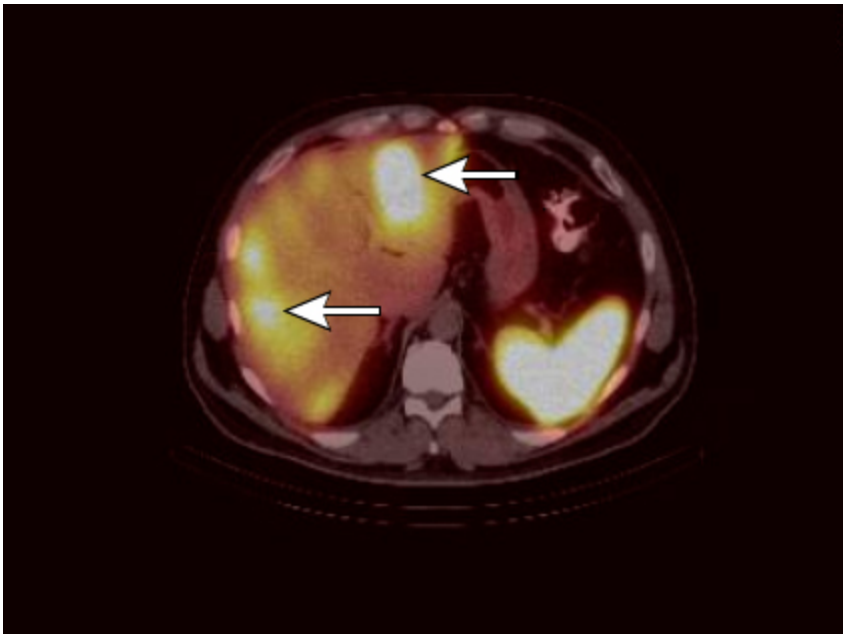


Computed tomography (CT) scan demonstrates a soft tissue mass containing coarse central calcifications (arrowhead) in the right lower quadrant. This neuroendocrine tumor is producing a characteristic desmoplastic response with spiculation of the adjacent mesenteric fat (arrow).

Courtesy of Jonathan Kruskal, MD, PhD.

Graphic 78186 Version 5.0

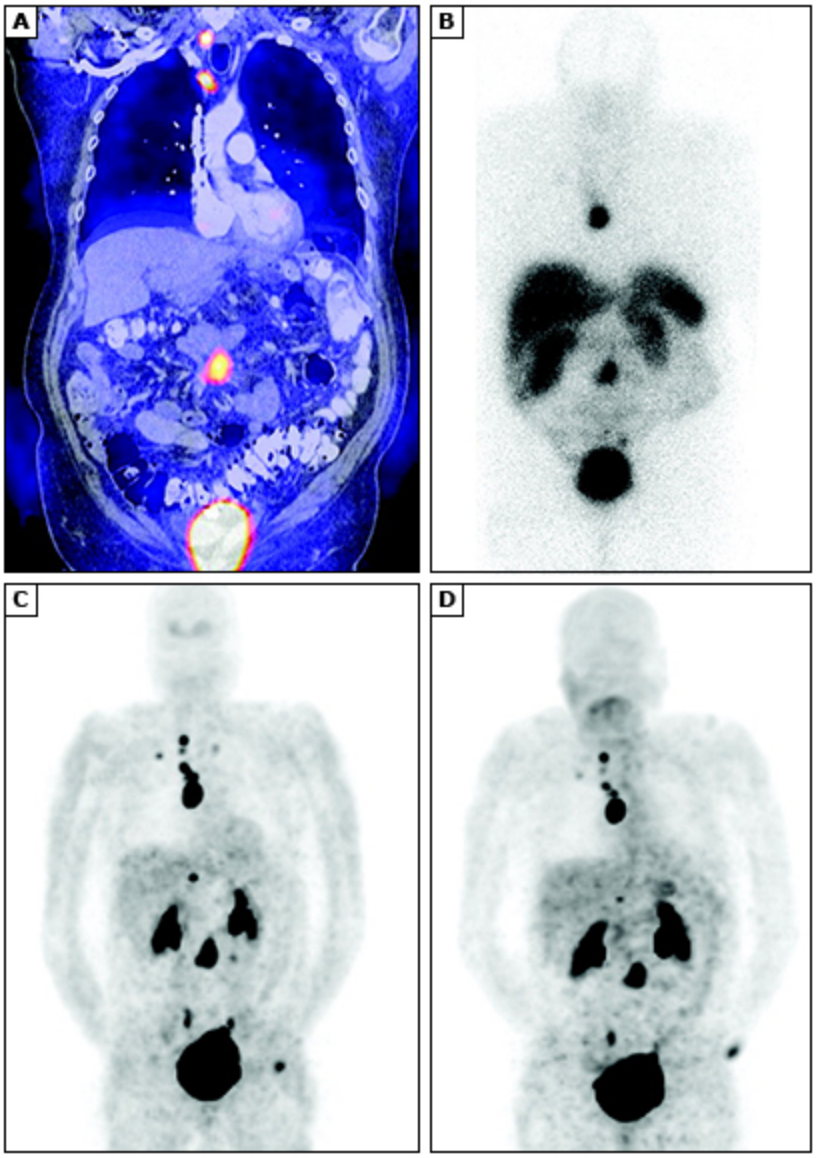
Liver metastases demonstrating high-grade radiotracer uptake on somatostatin receptor scintigraphy fused with SPECT/CT scan



SPECT: single photon emission computed tomography; CT: computed tomography.

Graphic 72923 Version 4.0

Functional PET imaging techniques for metastatic gastrointestinal tract neuroendocrine tumor



(A) Fused 18F-dihydroxy-phenyl-alanine (18F-DOPA) positron emission tomography (PET)/computed tomography scan

(B) Somatostatin receptor scintigraphy

(C) 18F-DOPA PET

(D) 11C-5-hydroxy-tryptophan (11C-5-HTP) PET of an 80-year-old male patient with metastatic neuroendocrine tumor of the gastrointestinal tract

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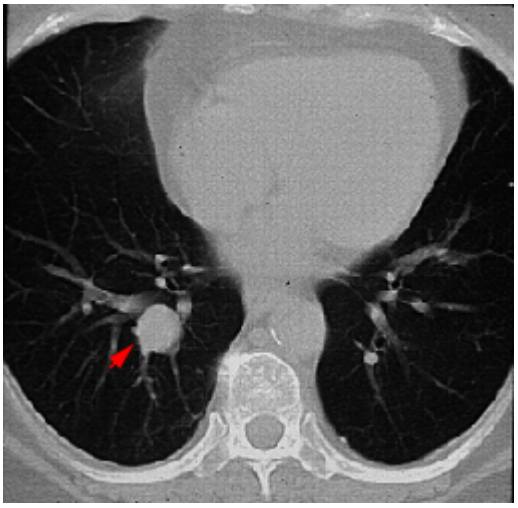
From: Koopmans KP, Neels OC, Kema IP, et al. Improved staging of patients with carcinoid and islet cell tumors with 18F-dihydroxy-phenyl-alanine and 11C-5-hydroxy-tryptophan positron emission tomography. J Clin Oncol 2008; 26:1489.

Graphic 81388 Version 6.0

Carcinoid tumor presenting as pulmonary nodule



Computed tomography (CT) scan showing smooth right lower lobe nodule, adjacent to the posterobasal segmental bronchus. This nodule was proven to represent a carcinoid tumor.

Courtesy of Paul Stark, MD.

Graphic 61692 Version 3.0

Contributor Disclosures

Jonathan R Strosberg, MD Grant/Research/Clinical Trial Support: ITM [NETs]; Novartis [NETs]; Radiomedix [NETs]; RayzeBio [NETs]. Consultant/Advisory Boards: Novartis [NETs]; Tersera [NETs]. Speaker's Bureau: Ipsen [NETs]. All of the relevant financial relationships listed have been mitigated. **Kenneth K Tanabe, MD** Patent Holder: EGF SNP to determine risk for HCC [Cirrhosis, hepatocellular carcinoma]; Use of EGFR inhibitors to prevent HCC [Cirrhosis, hepatocellular carcinoma]. Consultant/Advisory Boards: Cancer Expert Now [GI cancers, melanoma]; GSK [GI Cancers]; Imvax [GI cancers]; Leidos [Melanoma, GI cancers]; Teledoc [GI cancers, melanoma]. Other Financial Interest: American Cancer Society [Honoraria as editor of Cancer]. All of the relevant financial relationships listed have been mitigated. **David C Whitcomb, MD, PhD** Equity Ownership/Stock Options: Ariel Precision Medicine [Genetic testing]. Consultant/Advisory Boards: AbbVie [Pancreatic enzyme use]; Ariel Precision Medicine [Genetic testing]; BioNTech [Acute pancreatitis]; Nestle [Chronic pancreatitis]; Novartis [Chronic pancreatitis]; Organon [Pancreatic enzymes use]. All of the relevant financial relationships listed have been mitigated. **Sonali M Shah, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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