Could It Be a NET?

Neuroendocrine Tumors

Detecting and diagnosing an uncommon cancer
An uncommon cancer

Neuroendocrine neoplasms are a family of malignancies that are believed to originate in neuroendocrine cells found throughout the body. These include well-differentiated grade 1 (G1) and grade 2 (G2) neuroendocrine tumors (NET). Traditionally regarded as an indolent, slow-growing cancer, attention has been heightened around the rising incidence and malignant potential of these tumors.

Overview of 3 types of NET

This brochure focuses on NET arising in 3 key anatomic locations (gastrointestinal [GI] tract, lungs, and pancreas), providing an overview of their varying clinical presentations, techniques for their identification and evaluation, and diagnostic clues to help clinicians recognize them in practice.

NET are an uncommon cancer that can elude diagnosis for years, at which time disease often has metastasized, negatively impacting patient outcomes. Thus, a key unmet need is diagnosing patients earlier in the course of disease.

A word about neuroendocrine nomenclature

This brochure uses the nomenclature established in the 2010 WHO Classification of Tumours of the Digestive System, which establishes 2 broad types of neuroendocrine neoplasms:

- Neuroendocrine tumors (NET): well-differentiated neuroendocrine neoplasms that can be divided into grade 1 (G1) and grade 2 (G2) depending on proliferation and histology
- Neuroendocrine carcinomas: poorly differentiated grade 3 (G3) neuroendocrine neoplasms

NET may be referred to using a variety of terms, such as “carcinoids,” “carcinoid tumors,” or “endocrine tumors.” These terms can be used interchangeably with “NET” as defined above. NET may also be referred to by the hormones they secrete, such as gastrinoma (gastrin) or glucagonoma (glucagon).
Life-threatening potential

Diagnosis is often delayed

Well-differentiated NET can produce nonspecific symptoms that are easily mistaken for those of other conditions.\textsuperscript{4,5} This can delay the diagnosis of certain NET by up to 5 to 7 years.\textsuperscript{4}

Disease may be metastatic at diagnosis

NET often metastasize before they are diagnosed.\textsuperscript{6} In fact, 50\% of all patients in whom disease stage is reported have either regional or distant metastases at diagnosis.\textsuperscript{2} Notably, more than 60\% of patients with pancreatic NET have distant metastases at diagnosis. Frequent sites of metastasis include the lymph nodes, liver, and bones.\textsuperscript{7}

Even small GI and pancreatic NET (<2 cm) can be aggressive and metastasize.\textsuperscript{8,9}

<table>
<thead>
<tr>
<th>Primary NET Location</th>
<th>% of Patients With Metastatic Disease at Diagnosis</th>
<th>Median Survival Times (all disease stages, months)</th>
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<tbody>
<tr>
<td></td>
<td>Regional</td>
<td>Distant</td>
</tr>
<tr>
<td>Lungs</td>
<td>23</td>
<td>28</td>
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<tr>
<td>Pancreas</td>
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<td>Appendix</td>
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<tr>
<td>Duodenum</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Jejunum/ileum</td>
<td>41</td>
<td>30</td>
</tr>
<tr>
<td>Cecum</td>
<td>42</td>
<td>44</td>
</tr>
<tr>
<td>Colon</td>
<td>23</td>
<td>32</td>
</tr>
<tr>
<td>Rectum</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Life-threatening potential (cont)

Prognosis is poor with advanced disease

Long-term data (1973-2004) from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) database reveal the malignant potential of all neuroendocrine neoplasms. Survival rates vary according to disease stage, and even G1 and G2 NET have the potential to metastasize to distant sites, negatively impacting patient prognosis.

Grade also impacts prognosis

Along with disease stage, the grade of the neoplasm can also provide prognostic information. Grade estimates the biologic aggressiveness (ie, potential for metastatic spread) of the neoplasm. For example, G3 neuroendocrine carcinomas are highly aggressive, with a 5-year survival probability of 4% for patients with distant metastases. But even for well-differentiated G1 and G2 NET, the 5-year survival probability for patients with distant metastases is 35%.
Recognizing and evaluating NET

A disguised disease

NET are more prone to secrete hormones and overexpress biomarkers, such as chromogranin A and synaptophysin, than are high-grade neuroendocrine carcinomas. Some of the symptoms and syndromes associated with NET are due to excessive secretion of hormones and other bioactive substances. Other NET symptoms are due to neoplasm size or growth.

<table>
<thead>
<tr>
<th>Symptoms/Conditions</th>
<th>Biochemical testing</th>
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<tbody>
<tr>
<td><strong>Raise index of suspicion</strong></td>
<td><strong>Aid in differential diagnosis</strong></td>
</tr>
<tr>
<td>• Abdominal pain/cramping</td>
<td></td>
</tr>
<tr>
<td>• Diarrhea/steatorrhea</td>
<td></td>
</tr>
<tr>
<td>• Constipation/abdominal pain</td>
<td></td>
</tr>
<tr>
<td>• Anorexia, nausea, vomiting</td>
<td></td>
</tr>
<tr>
<td>• Wheezing</td>
<td></td>
</tr>
<tr>
<td>• Zollinger-Ellison syndrome (ZES)</td>
<td></td>
</tr>
<tr>
<td>• Hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>• Dermatitis</td>
<td></td>
</tr>
<tr>
<td>• Cushing disease</td>
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</tbody>
</table>

NET are more prone to secrete hormones and overexpress biomarkers, such as CgA and SNAP, than are high-grade neuroendocrine carcinomas.

<table>
<thead>
<tr>
<th>Hormone tests</th>
<th>Tumor biomarkers</th>
</tr>
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<tbody>
<tr>
<td>5-HIAA (24-hour urine sample)</td>
<td>CgA</td>
</tr>
<tr>
<td>Glucose and insulin (72-hour fasting glucose)</td>
<td>NSE</td>
</tr>
<tr>
<td>Fasting serum gastrin/gastric pH</td>
<td>SNAP</td>
</tr>
<tr>
<td>Plasma glucagon, VIP, somatostatin</td>
<td></td>
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</tbody>
</table>

*Tumor biomarkers typically are more strongly expressed in NET than in other neuroendocrine neoplasms.*

CgA, chromogranin A; 5-HIAA, 5-hydroxyindoleacetic acid; NSE, neuron-specific enolase; SNAP, synaptophysin; VIP, vasoactive intestinal peptide.
Recognizing and evaluating NET (cont)

Because these symptoms often are associated with more common conditions, identifying and diagnosing a NET may be challenging. However, tools are available to help establish a diagnosis and monitor existing NET.

For diagnostic accuracy — as well as continued disease management — preliminary biomarker results should be confirmed with imaging and endoscopic techniques, along with histopathologic analysis, when appropriate.7,18

Localize and Characterize

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Endoscopy</th>
<th>Pathology</th>
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<tbody>
<tr>
<td>Localize primary neoplasm and metastases11,18</td>
<td>Locate neoplasms, collect biopsy samples11,18</td>
<td>Identify and grade NET19</td>
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<tr>
<td>• Triple-phase CT</td>
<td>• Endoscopy</td>
<td>• Immunohistochemical staininga</td>
</tr>
<tr>
<td>• MRI</td>
<td>• Endoscopic ultrasound</td>
<td>— CgA</td>
</tr>
<tr>
<td>• Somatostatin receptor scintigraphy (Octreoscan™)</td>
<td></td>
<td>— SNAP</td>
</tr>
<tr>
<td>• MIBG scintigraphy</td>
<td></td>
<td>Definitive diagnosis requires tissue confirmation, when appropriate</td>
</tr>
<tr>
<td>• PET</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aTumor biomarkers typically are more strongly expressed in NET than in other neuroendocrine neoplasms.4,5,10,11

CT, computed tomography; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; PET, positron emission tomography.

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Could it be a lung NET?

The basics

G1 and G2 NET of the lung — called typical and atypical lung carcinoids — account for approximately 2% of all primary lung tumors. About one-third of diagnosed lung NET exhibit atypical histologic features.

Hormones secreted include adrenocorticotropic hormone (ACTH), growth hormone–releasing hormone (GHRH), and antidiuretic hormone (ADH). Carcinoid syndrome is a rare manifestation, but can occur in the presence of metastatic disease.

Lung NET are slightly more prevalent in women vs men and in whites vs other ethnicities, and are the most common primary lung tumor in children and adolescents.

Typical vs Atypical Carcinoids

Typical carcinoid
- Usually present in the fifth decade of life
- Most often central in location
- Rarely associated with the classic carcinoid syndrome; have been associated with ectopic ACTH secretion, resulting in Cushing syndrome

Atypical carcinoid
- Occur most commonly in the sixth decade of life
- More common in smokers
- Tend to be larger in size and more commonly peripheral in location than typical carcinoids
- Often found incidentally
- Characterized by the presence of frequent mitoses or areas of necrosis

Clinical presentation

Patients are often asymptomatic for long periods, or may present with nonspecific symptoms, including coughing and wheezing. Other symptoms include dyspnea, hemoptysis, recurrent obstructive pneumonia, pleuritic pain, and atelectasis. Related syndromes due to hormonal secretion are Cushing syndrome, acromegaly, and hyponatremia.

Respiratory symptoms are typically only encountered with centrally located lung NET.
Diagnostic considerations

Nonspecific symptoms such as coughing and wheezing can prompt initial suspicion of asthma, contributing to delayed diagnosis.25

Symptoms of Cushing syndrome are seen in approximately 2% of patients with lung NET.26

Evaluation for Cushing syndrome may be warranted in patients presenting with symptoms of hypercortisolemia.

Recommended tests include: overnight 1-mg dexamethasone suppression test with 8 AM plasma cortisol; 2 to 3 midnight salivary cortisols; or free cortisol in a 24-hour urine sample.7

Importantly, assess serum ACTH in these patients because elevated levels indicate the excessive cortisol is not due to adrenal gland dysfunction and may point to an ectopic lung NET as the cause.7

Radiologic investigations should focus on the major bronchi (main-stem and lobar bronchi) and the peripheral lung (segmental bronchi or beyond).26

Immunohistochemical staining of select markers (eg, chromogranin A, synaptophysin) can help confirm the neuroendocrine nature of resected/biopsied tumor specimens, but do not distinguish typical and atypical histologies.23

For more information on lung NET, visit www.neuroendocrinetumor.com or ask your Novartis representative about Lung Neuroendocrine Tumors: An Overview of the Disease and Its Management.
Could it be a pancreatic NET?

The basics

Most pancreatic NETs are well-differentiated G1 or G2 tumors\textsuperscript{27,28} that vary in clinical presentation and aggressiveness.\textsuperscript{14,29} They can be sporadic or associated with genetic syndromes such as multiple endocrine neoplasia type 1 (MEN-1), von Hippel-Lindau syndrome (VHL), von Recklinghausen disease (neurofibromatosis [NF-1]), and tuberous sclerosis complex (TSC).

Most pancreatic NETs are nonfunctional; however, they may be associated with symptoms and syndromes due to the oversecretion of specific hormones.\textsuperscript{14,30}

Clinical presentation

Abdominal pain is one of the most common presenting symptoms. Symptoms of hormone oversecretion typically are not part of the initial presentation and are usually indicative of metastatic disease.\textsuperscript{31}

Diagnostic considerations

Patients with pancreatic NET are more likely to have advanced disease at diagnosis than patients with other types of NET.\textsuperscript{2}

Liver metastases occur much more frequently with gastrinomas located in the pancreas (typically >1 cm) than in the duodenum (typically <1 cm).\textsuperscript{32}

Elevated serum gastrin levels in some patients in whom a pancreatic NET is suspected (ie, gastrinoma) may be confounded by achlorhydria, antacids, or proton pump inhibitor (PPI) therapy.\textsuperscript{7}

Endoscopic ultrasound can localize most pancreatic NET, although multiphase CT or MRI should be used to identify metastatic disease.\textsuperscript{7}

For more information on pancreatic NET, visit www.neuroendocrinetumor.com or ask your Novartis representative about \textit{Pancreatic Neuroendocrine Tumors: An Overview of the Disease and Its Management}. 
<table>
<thead>
<tr>
<th>MOST COMMON TYPES OF PANCREATIC NET</th>
<th>Pancreatic NET</th>
<th>Signs and Symptoms</th>
<th>Diagnostic Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulinoma</strong></td>
<td>Hypoglycemia</td>
<td>A standard 72-hour fasting test should be used to measure glucose (&lt;45 mg/dL) and insulin (&gt;30 pmol/L) levels and to exclude all differential diagnoses of insulinoma, except for very rare conditions. Measurement of proinsulin and C-peptide levels may be helpful.</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrinoma</strong></td>
<td>Recurrent peptic ulcer, abdominal pain, diarrhea (Zollinger-Ellison syndrome, or ZES)</td>
<td>Diagnosis often begins with determination of fasting serum gastrin levels (≥1000 pg/mL) and gastric pH (&lt;2.5). Over repeated testing, &lt;0.5% of patients with ZES will have normal values. Note: PPI therapy can elevate serum gastrin levels and should be stopped at least 1 week before testing patients suspected of gastrinoma.</td>
<td></td>
</tr>
<tr>
<td><strong>Glucagonoma</strong></td>
<td>Diabetes/glucose intolerance, rash (migratory necrolytic erythema), thromboembolic disease</td>
<td>Diagnosis can be made when plasma glucagon levels are increased to 500 pg/mL to 1000 pg/mL (normal range &lt;50 pg/mL).</td>
<td></td>
</tr>
<tr>
<td><strong>VIPoma</strong></td>
<td>Severe watery diarrhea, electrolyte disturbances (Verner-Morrison syndrome, pancreatic cholera, or watery diarrhea, hypokalemia, and achlorhydria [WDHA] syndrome)</td>
<td>Diagnosis is based on elevated levels (&gt;200 pg/mL) of plasma VIP in patients with large-volume secretory diarrhea (&gt;700 mL/d).</td>
<td></td>
</tr>
<tr>
<td><strong>Somatostatinomas</strong></td>
<td>Diabetes, cholelithiasis, diarrhea</td>
<td>Diagnosis can be confirmed by elevated plasma somatostatin levels in the setting of a histologically confirmed NET.</td>
<td></td>
</tr>
</tbody>
</table>
Could it be a GI NET?

The basics

Within the GI tract, most NET arise in the small intestine (jejunum/ileum; 41.8%), rectum (27.4%), and stomach (8.7%).

NET of the duodenum, jejunum/ileum, and rectum occur significantly more frequently in men than in women.

Carcinoid syndrome can be a primary clinical manifestation of NET and is most frequently associated with NET of the small intestine.

Some GI NET are often discovered incidentally during routine endoscopic procedures of the stomach, colon, rectum, and small intestines.

Clinical presentation

The most common signs and symptoms experienced by patients with carcinoid syndrome are flushing, diarrhea, abdominal cramping, and cardiac disease caused by valvular heart lesions. Symptoms typically do not manifest until the tumor metastasizes.

Carcinoid syndrome is also associated with skin changes such as telangiectasia, cyanosis, and, rarely, pellagra.

For more information on GI NET, visit www.neuroendocrinetumor.com or ask your Novartis representative about Gastrointestinal Neuroendocrine Tumors: An Overview of the Disease and Its Management.

### Symptoms of Carcinoid Syndrome and Their Frequency

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Patients With Symptoms, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing</td>
<td>90</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>70</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>40</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>40-45</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>25</td>
</tr>
<tr>
<td>Wheezing</td>
<td>15</td>
</tr>
<tr>
<td>Pellagra</td>
<td>5</td>
</tr>
</tbody>
</table>
Clues That Could Indicate Carcinoid Syndrome

**Flushing** in carcinoid syndrome is characteristically dry (not associated with perspiration) and usually pink to red in color, affecting the face, neck, and upper torso.\(^{11,43,44}\) Transient hypotension, headache, and bronchoconstriction may coincide with flushing.\(^{11,44}\)

**Carcinoid heart disease** usually involves the right-side valves and develops later in the disease process. The right side of the heart is exposed to high levels of serotonin and other vasoactive substances released from hepatic metastases, causing the thickening, retraction, and fixation of the pulmonary and tricuspid valves. This can lead to valvular dysfunction and, eventually, right-sided heart failure.\(^{3,11,37,41,44-46}\)

**Abdominal pain** in carcinoid syndrome typically is intermittent and crampy, and may not be relieved with defecation as it can be in irritable bowel syndrome (IBS).\(^{39,47}\)

**Diarrhea** associated with carcinoid syndrome is typically chronic and may be nocturnal. It is characterized by increased gut motility and watery stools resulting from intestinal hypermotility and hypersecretion. Fasting typically does not alleviate the diarrhea.\(^{39,48,49}\)

**Diagnostic considerations**

Assessment of 24-hour urinary 5-HIAA is a useful diagnostic tool for NET associated with carcinoid syndrome\(^ {11}\) and can be used to monitor response to treatment.\(^ {7,41,42}\) Carcinoid heart disease has also been associated with elevated levels of urinary 5-HIAA.

The symptoms of carcinoid syndrome can have a major effect on quality of life, and earlier diagnosis can help patient outcomes.
Collaborative approach to patient care

**NET may require collaboration among specialists from multiple disciplines**

The appropriate management of NET is dependent on factors such as:

- Location of neoplasm and specific glands involved
- Grade of neoplasm
- Differentiation of neoplasm cells
- Aggressiveness and stage of neoplasm
- Amount of hormones produced
- Specific patient needs
- Comorbidities/clinical manifestations involved

Because numerous health care professionals can contribute to the optimal care of patients with NET, the NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) state: *Appropriate diagnosis and treatment of neuroendocrine tumors often involves collaboration between specialists in multiple disciplines using specific biochemical, radiologic, and surgical methods.*

**The multidisciplinary team may include**

- Dietitians
- Endocrinologists
- Gastroenterologists
- Interventional radiologists
- Nuclear medicine experts
- Nurses
- Oncologists
- Pathologists
- Pulmonologists
- Social workers/case managers
- Surgeons

Furthermore, institutional studies show that outcomes are improved for patients who are managed at centers that specialize in NET.
References


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Neuroendocrine Tumors: The unique challenges of a complex disease

A cancer on the rise\textsuperscript{1,2} 
- Incidence of all neuroendocrine neoplasms is increasing dramatically—fivefold over the past 30 years\textsuperscript{2}

Life-threatening potential may be overlooked 
- Because NET can produce vague, nonspecific symptoms,\textsuperscript{8} the estimated time to diagnosis can reach 5 to 7 years\textsuperscript{6} 
- Patients with distant metastases have a median survival of 33 months\textsuperscript{2} 
- The 5-year survival rate is 35% for patients diagnosed with well-differentiated grade 1 or grade 2 NET with distant metastases\textsuperscript{2}

Detection and diagnosis are key 
- Imaging techniques such as CT, MRI, and somatostatin receptor scintigraphy can help confirm an initial NET diagnosis and monitor disease status\textsuperscript{10} 
- Biochemical tests that detect bioactive substances secreted by NET have diagnostic and prognostic significance\textsuperscript{34}

Multidisciplinary approach helps ensure optimal patient care 
- Appropriate management of NET often involves collaboration between specialists in multiple disciplines using specific biochemical, radiologic, and surgical methods\textsuperscript{10}