Carcinoid Syndrome - Research Perspective

Introduction

Carcinoid syndrome is a collective of symptoms that occurs in patients with Carcinoid tumor. It is caused by excessive endogenous secretion of hormones mainly serotonin and kallikrein. The syndrome includes flushing and diarrhea, and, less frequently, heart failure and bronchoconstriction. Carcinoid tumors arise from neuroendocrine cells, which are widespread in the human body, especially in the organs derived from the primitive intestine. (1, 2, 3)

In 1980, the World Health Organization (WHO) applied the term carcinoid to all tumors of the diffuse endocrine system (synonymous with amine precursor uptake and decarboxylation [APUD] and neuroendocrine cell system).

The carcinoid syndrome is seen in approximately 10% of carcinoid tumors and the symptoms appear when the vasoactive substances from the tumors enter the systemic circulation escaping hepatic degradation. Typically, 90% of carcinoid tumors originate from the distal ileum or appendix (the embryologic midgut); carcinoid tumors represent 90% of appendiceal tumors. (1, 2, 3)

Four key symptoms of carcinoid syndrome

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Chronic diarrhea and carcinoid syndrome

Chronic diarrhea is seen up to 80% of patients with carcinoid syndrome. There are many causes of chronic diarrhea; however, certain characteristics may help identify this symptom with carcinoid syndrome. (9)

The stools in carcinoid syndrome are watery and result from intestinal hypermotility and hypersecretion. The increase in gut motility in patients with carcinoid syndrome is likely to be caused by serotonin, which is released as part of carcinoid syndrome (11) and stimulates small bowel and colonic secretions and motility. (11)

"A clue to carcinoid syndrome is that fasting does not reduce the diarrhea, because the increased motility and increased secretion are independent of intake." – Dr David C Metz.

Another clue is that diarrhea may be nocturnal. (12) Nocturnal diarrhea may be observed in other conditions (e.g., IBD), but it is typically not seen in IBS. If IBD is suspected clinically, the patient can be evaluated endoscopically and/or radiologically.

Abdominal pain and carcinoid syndrome

Abdominal pain is a nonspecific symptom with many different potential causes. Diagnosing abdominal pain associated with carcinoid syndrome is difficult, as there are no real distinguishing factors. In carcinoid syndrome, abdominal pain or discomfort may be due to gut hypermotility, obstructive-type symptoms or, rarely, tumor intussusception. Pain may also be due to serosal involvement of the tumor or stretching of the liver capsule because of large hepatic metastases.

Abdominal pain in carcinoid syndrome is intermittent and crampy, and occurs in approximately 40%–51% of patients. Pain associated with diarrhea in carcinoid syndrome may be colicky and may not be relieved with defecation. (13)

Flushing and carcinoid syndrome

Flushing is the most common symptom of carcinoid syndrome and occurs in more than 90% of patients. Usually pink to red in color, flushing typically affects the face, neck, and upper trunk. Flushing in carcinoid syndrome is characteristically dry - in women, this helps distinguish it from menopausal hot flashes, which are often associated with perspiration. The specific cause of flushing in carcinoid syndrome is unknown, although it has been shown to be preceded by a rise in substance P.

Transient hypotension, headache, and bronchoconstriction may coincide with flushing in patients with carcinoid syndrome, particularly in those with foregut NETs. Physicians should consider that menopausal hot flashes are not associated with a fall in blood pressure. (14)

Cardiac disease and carcinoid syndrome

Cardiac disease is one of the most serious aspects of this disease, occurring in approximately two-thirds of patients with carcinoid syndrome. (14) Carcinoid heart disease can be detected with 2-dimensional echocardiographic and Doppler examinations. A combination of tricuspid and pulmonary lesions is characteristic of carcinoid heart disease.

1. Epidemiology

United States

Probably 7-8 cases of carcinoid are diagnosed in the United States per year, but the actual frequency is almost certainly higher, because many patients never develop the related syndrome. Some researchers estimate that the incidence may be 1-2 cases per 100,000 individuals.
**International**

Epidemiologic studies have reported incidences of carcinoid tumors ranging from 0.79 to 1.88 per 100,000 population; a study from the Netherlands found an incidence of 1.95 per 100,000 population. These numbers are probably underestimates, because a large number of affected individuals do not develop the related syndrome. A Swedish autopsy study reported an incidence of 8.4 cases per 100,000 population. Carcinoid tumors are discovered in approximately 1-2 appendectomy cases per 200-300 per year.\(^{(34, 35)}\)

**Mortality/Morbidity**

Tumors that are smaller than 1 cm in diameter rarely metastasize, while lesions larger than 2 cm often metastasize. The presence of a few small metastases to the liver is associated with a longer life expectancy. Morbidity is related to vasoactive amine production. The survival rate usually correlates inversely with the levels of daily urinary 5-HIAA excretion. Death is usually caused by cardiac or hepatic failure and by complications associated with tumor growth. Factors associated with higher mortality are high plasma levels of neuropeptide K and chromogranin A, location of the tumor in the large bowel, advanced disease, and a concomitant second malignancy. Mucus-producing tumors developing in the appendix also have some malignant characteristics.\(^{(34, 35)}\)

**Race:** No racial prevalence is known.

**Sex:** This syndrome affects men and women equally.

**Age:** Carcinoids occur most frequently in patients aged 50-70 years. Age at diagnosis ranges from 10-93 years (mean age 55 y).

**Prevalence of NETs**

Most neuroendocrine tumors, like other tumors, are clinically silent, producing symptoms only as a consequence of tumor growth. But silence should not be mistaken for a low disease prevalence. In fact, NETs are more prevalent than many gastrointestinal (GI) malignancies.

**Prevalence of NETs compared with other cancers.\(^{(4, 5)}\)**

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon &amp; Rectum</td>
<td>1,141,407</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>103,312</td>
</tr>
<tr>
<td>Stomach</td>
<td>65,836</td>
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<tr>
<td>Pancreas</td>
<td>28,664</td>
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<tr>
<td>Esophagus</td>
<td>21,427</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>32,353</td>
</tr>
</tbody>
</table>

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The majority of NETs occur in the GI tract (67.5%) and the bronchopulmonary system (25.3%). Within the GI tract, most NETs occur in the small intestine (41.8%), rectum (27.4%), and stomach (8.7%). Less than 1% of NETs occur in the pancreas, although this number is typically considered to be low because nonmalignant tumors (ie, insulinomas and small, nonfunctioning pancreatic NETs) have not been included in Surveillance, Epidemiology, and End Results (SEER) Program registries. 

Pancreatic NETs also account for only 1% of pancreatic cancers by incidence, while representing 10% of all pancreatic cancers by 28-year limited duration prevalence. Again, however, both of these numbers may be underestimated in SEER databases.

While some studies indicate that roughly half of all pancreatic NETs are nonfunctional, this number may be underreported. In fact, 85% of pancreatic NETs reported in SEER registries have an unknown functional status. Among pancreatic NETs with known functional status, gastrinomas account for 6%, insulinomas 4%, glucagonomas 2%, and VIPomas 1%.

Although the bronchopulmonary system is a frequent site of NETs, grade 1 and grade 2 (G1/G2) bronchial NETs - also called typical and atypical lung carcinoids, respectively - represent only 1% to 2% of all lung cancers, with an annual age-adjusted incidence of 1.35 per 100,000 individuals. Annual age-adjusted incidence for thymic NETs is 0.02 per 100,000 individuals.

Complex malignancies on the rise

A SEER database analysis shows a dramatic 5-fold increase in diagnosed incidence of NETs from 1973 to 2004 (see chart). A continued increase in reported incidence is predicted.
2. Risk factors

Risk of metastasis correlates with size of primary tumor, as follows:

3. Etiology

Similar to many other cancers, the exact cause is unknown. Malignant carcinoid syndrome does not generally appear to be hereditary.

A study of genetic alterations in small bowel carcinoid tumors found that loss of all or most of chromosome 18 was the most common finding. Heterozygosity was also lost on chromosome arms 9p and 16q. Although the amplitude of observed gains was modest in comparison with those reported in some other tumor types, one focal region of recurrent gain on 14q mapped to the locus of the gene encoding the antiapoptotic protein DAD1.16

4. Diagnosis

Diagnosing Carcinoid tumors can be a challenge. The appropriate use of biomarker testing may be helpful in diagnosing Carcinoid tumors, even in the absence of a secretory syndrome. Initial indications should then be confirmed by additional imaging and/or endoscopic techniques, biochemical evaluation, and biopsy, as appropriate. A wide range of additional tools also support your diagnostic efforts, and new imaging and biochemical testing techniques continue to be developed and refined by researchers. Click on any of the descriptions below to learn more.

**Biomarkers**

**Chromogranin A (CgA):** Up to 90% of patients with NETs have elevated CgA levels.
5-Hydroxyindoleacetic acid (5-HIAA): Has diagnostic and prognostic value in NETs associated with carcinoid syndrome.(23)

Plasma neuronal specific enolase (NSE): A useful circulating marker for poorly differentiated NETs, where NSE sensitivity exceeds 70% and specificity can reach 85%. (24)

Imaging

Computed tomography (CT): A widely available tool for the localization and staging of solid tumors, including Carcinoid tumors.(19)

Magnetic resonance imaging (MRI): A well-recognized imaging technique, useful in the localization of NETs and their metastases.(19, 20)

Octreoscan™: A unique, whole-body imaging technique that identifies primary NETs and metastases that express somatostatin receptors.(21)

Octreoscan is a trademark of Covidien AG or one of its affiliates.

131Iodine metaiodobenzylguanidine (MIBG) scintigraphy: Uses an injected radioisotope to locate and monitor primary and/or metastatic pheochromocytoma and neuroblastoma, as well as certain other NETs.(22)

Endoscopic Techniques

GI endoscopy: A number of endoscopic techniques may allow visualization of GI lesions, particularly in the stomach, duodenum, and rectum.

Endoscopic ultrasound: A relatively noninvasive technique with low morbidity that helps visualizes pancreatic NETs. (25)

Hormone Tests

Biochemical tests targeting substances secreted by functional pancreatic NETs can be useful for diagnosis. (26)

5. Treatment

NETs are complex cancers with the potential to involve multiple co morbidities. Management of a NET may depend on factors such as tumor size, grade, stage, location, secretory status, and potential associated symptoms, if any. Gathering input from a multidisciplinary team gives physicians an opportunity to improve outcomes. (27)

Among the treatment options that may be considered on a patient-by-patient basis are:

- Surgery with curative intent for localized NETs. Surgery can also play a palliative role in certain metastatic patients
- Chemotherapy and other systemic agents
- Targeted radionuclide therapy
- Radiofrequency ablation and chemoembolization to address hepatic metastases
- Clinical trial participation.

Surgery

The aim of any cancer treatment should be curative where possible. Surgery is the only curative treatment currently available for NETs.(27) First-line treatment usually involves surgical resection of the primary tumor and associated nodal disease.
Before surgical resection of functional pancreatic NETs, symptoms of hormonal excess must be treated. Recommended management of the symptoms of hormonal hypersecretion depends on the hormone secreted. For example, glucose levels in patients with insulinomas should be stabilized with diet and/or diazoxide. Gastrin hypersecretion in patients with gastrinomas may be treated with proton pump inhibitors (PPIs).\(^{(28)}\)

Patients who already have advanced-stage NETs present unique surgical challenges. Operative therapy is rarely curative in the setting of metastatic disease, but it can have an important role in achieving palliation in selected patients.\(^{(30)}\)

Surgical debulking may be an option in appropriate patients for relief of symptoms; indeed, it may be the only option for patients with life-threatening symptoms due to hormonal excess for which other approaches have proven ineffective. Patients with advanced-stage NETs may also benefit from a multidisciplinary combination of surgery and other interventions.\(^{(31)}\)

**Surgery for hepatic metastases**

**Chemotherapy and other systemic agents**

The role of cytotoxic chemotherapy is changing with the increasing realization that slow-growing GI NETs generally respond poorly to this treatment modality. However, the technique is considered a viable treatment option for inoperable or poorly differentiated tumors, particularly where metastases and angioinvasion are present.\(^{(28, 32)}\)

**Targeted radionuclide therapy**

131I-MIBG is currently the only licensed therapy that serves as a palliative option for certain patients with inoperable or metastatic tumors. The use of this treatment modality has been limited by the fact that the uptake of isotope by some tumors is insufficient for the treatment to be effective. Other forms of targeted radionuclide therapy are currently under development.

**Radiotherapy**

- Radiofrequency ablation (RFA): Randomized clinical trials are needed to further our understanding of the use of RFA in managing NETs. But the technique is recommended to stabilize or reduce the size of nonresectable tumors, including hepatic metastases in which embolization has not been effective. It may also have a role in reducing hormone secretion functional metastatic tumors. However, because neuroendocrine metastases often are small and numerous, treatment may require multiple sessions over several years.\(^{(28)}\)
- External beam radiation: Although evidence suggests that carcinoid tumors may be resistant to radiation therapy, the technique may alleviate bone pain due to metastases.\(^{(28, 29)}\)

**Key points to consider when developing a management plan for NET patients**

- Location of the primary tumor
- Stage and extent of metastases
- Tumor grade and histology
- Secretory activity of the tumor
- Symptoms and comorbidities
- Other factors, such as quality of life and personal considerations

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6. Clinical trials

Globally more than 59 studies in carcinoid syndrome have been done till date, among them 47 studies in USA, 9 in Europe, 3 in Canada, 3 in Middle east, 2 in North asia, 2 in pacific and one study in East asia, South asia and South east asia with one study respectively. (33)

Because of the rarity of carcinoid syndrome and complexity of the symptoms, many patients remain undiagnosed until well into the late stages of the illness, at the time when their carcinoid syndrome becomes apparent.

With the increase in clinical awareness, carcinoid will become increasingly identified, often at an earlier stage in the course of the disease. This review provides brief information in detecting and assessing advanced carcinoid disease, and then continues to discuss strategies (both potentially curative and palliative) to control symptoms, at earlier stages and improve quality of life for these patients.

References

05. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology; Neuroendocrine tumors. V2.2010..

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DRAXIMAGE MIBG [package insert]. Kirkland, Quebec, Canada: DRAXIMAGE, a division of DRAXIS Specialty Pharmaceuticals Inc; March 2006.


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