

## **Update on Neuroendocrine Tumors of the GI Tract**

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Neuroendocrine tumors develop throughout the gastrointestinal tract from the esophagus to the anus, but they are decidedly unusual in the esophagus and anus. These tumors include a spectrum of lesions that encompasses everything from endocrine cell hyperplasia through carcinoid tumors to small cell carcinomas or neuroendocrine carcinomas. The term carcinoid tumor encompasses a wide spectrum of different neoplasms that originate from various neuroendocrine cells. These tumors are referred to as carcinoid tumors or they may be referred to by the name of the cell population constituting them or by the hormones that they produce. Similar neoplasms in the pancreas are usually referred to as islet cell tumors.

Gastrointestinal neuroendocrine tumors arise in the setting of two genetic susceptibility syndromes: multiple endocrine neoplasia type-1 and neurofibromatosis type-1. Patients with MEN-1 have a mutation or deletion in the tumor suppressor gene MEN-1 that localizes to 11-13 and encodes a nuclear protein menin. ECL carcinoids constitute an integral component of the MEN-1 syndrome and gastric carcinoids arise in 13-30% of patients with familial MEN-1 and Zollinger Ellison Syndrome (ZES). Patients with neurofibromatosis type 1 typically develop a number of periampullary neoplasms, including somatostatinomas and gangliocytic paragangliomas.

In some cases carcinoid tumors arise on a background of endocrine cell hyperplasia of a similar cell type. This suggests that a relationship exists between the endocrine cell hyperplasia and subsequent development of a carcinoid tumor. Examples of this phenomenon include the ECL Type 1 and Type 2 carcinoid tumors arising on a background of ECL cell hyperplasia, duodenal gastrinomas arising on a background of G cell hyperplasia and somatostatinomas arising in a area of somatostatin cell hyperplasia.

### **CARCINOID TUMORS**

#### **General Features**

Generally the clinical features of carcinoid tumors are vague or absent unless the tumor is large enough to create a mass effect or it secretes bioactive mediators that create specific syndromes, such as the carcinoid syndrome or ZES. Patients with esophageal tumors may seek care because of dysphagia, weight loss, reflux esophagitis and chest pain. Most gastric endocrine cell tumors arise in the setting of hypergastrinemia causing the patient to present with peptic ulcer disease or chronic gastritis. More distally located gastric tumors may cause gastric outland obstruction. Most duodenal endocrine tumors become symptomatic by producing mass lesions that cause bleeding and intestinal obstruction or that block the common bile duct or pancreatic duct, causing obstructive jaundice or pancreatitis respectively. Weight loss, diarrhea, lymphadenopathy or the carcinoid syndrome may also occur. Many symptomatic patients with distal small intestinal tumors

have a long history of intermittent crampy abdominal pain suggestive of episodic intestinal obstruction. As the symptoms worsen, with progressive intestinal obstruction, abdominal distention and vomiting develop. Approximately 5% of patients develop signs of intestinal infarction secondary to intussusception, volvulus or vascular disease.

The carcinoid syndrome develops in fewer than 10% of patients with small intestinal ECL carcinoids, usually in patients with hepatic metastasis.

Most appendiceal endocrine tumors are incidental findings in appendectomy specimens. Tumors that arise proximally may obstruct the lumen, producing appendicitis. Patients with colonic carcinoid tumors tend to seek care late in life with anorexia, weight loss, weakness, abdominal pain or liver metastasis. Rectal carcinoids typically manifest with constipation or pain or bleeding, usually due to trauma associated with the passage of solid feces over the tumor. However, it is important to note that approximately 50% of all patients with rectal carcinoids remain asymptomatic and the lesions are often detected as incidental findings during screening endoscopies.

Grossly, carcinoid tumors tend to be firm, submucosal nodules that usually measure <2 cm in diameter, developing at the mucosal/submucosal junction. The overlying mucosa usually remains intact or it may become slightly eroded. The tumors range from barely palpable, tan-yellow or gray-grown thickenings to nodules that measure >3.5 cm. These tumors grow slowly and extend into the underlying submucosa and overlying mucosa. As they grow, they may infiltrate locally beyond the submucosa into the muscularis propria, eventually reaching the external surface of the gut. As the tumors become more deeply invasive, fibrosis develops and can cause angulation, kinking, or distortion of the bowel wall, eventually resulting in obstruction. Blood vessels may be caught in the fibrosing process and then secondarily compressed, leading to ischemia.

### **Histological Features**

Gastrointestinal carcinoid tumors can be divided into five histological patterns:

1. Solid, nodular and insular chords;
2. Trabecular or ribbons with frequent anastomosing patterns;
3. Tubules and glands or rosette-like patterns;
4. Poorly differentiated or atypical patterns;
5. Mixed tumors.

The classical carcinoid tumor is one that arises in the mid-gut from serotonin-producing Kulchitsky cells.

Most **esophageal carcinoid** tumors contain anastomosing ribbons, solid nest trabecular and acinar or rosettes, although mixed patterns with more typical solid nests may be seen. In patients with **gastric ECL** type tumors, multifocal gastric ECL cell micronests and multifocal carcinoid tumors develop in the atrophic and metaplastic gastric body. Some patients have coexisting adenocarcinomas and multiple carcinoid tumors.

ECL carcinoids are divided into Type 1, Type 2 and Type 3. The Type 1 carcinoid is characterized by the presence of multiple small fundic tumors limited to the mucosa and submucosa associated with ECL cell hyperplasia arising on a background of autoimmune chronic atrophic gastritis. Type 2 ECL cell carcinoids are associated with MEN-1. Type 3 ECL carcinoids are sporadic lesions having no association with autoimmune chronic atrophic gastritis, MEN-1 or the ZES. There is no association with adjacent ECL cell hyperplasia. In patients with ECL Type 1 tumors, there is a background of endocrine cell hyperplasia.

The individual stages of hyperplasia are distinguished as simple, linear, micronodular and adenomatoid. All of these exhibit intact basement membranes. As each micronodule enlarges, the basement membrane breaks down and cytological atypia and increased nuclear cytoplasmic ratios develop. These lesions are dysplastic and show morphologic variations as enlarging micronodules, fusing micronodules, microinvasive lesions or nodules with a newly formed stroma. The latter occur when the nodules acquire a lobular or trabecular pattern. Lesions initially remain completely intramucosal. Both Type 1 and Type 2 ECL carcinoids consist of small, microlobular trabecular aggregates formed by regularly distributed cells arranged in a mosaic pattern with regular monomorphic nuclei, non prominent nucleoli and abundant eosinophilic cytoplasm. Mitosis and lymphatic invasion are usually absent. More advanced lesions can invade the vascular or lymphatic channels, leading to nodal or distant metastases.

**Sporadic ECL carcinoids** are solid cellular aggregates with large trabecular and cellular crowding. There is an irregular distribution of round, spindle shaped and polyhedral cells. The nuclei tend to be large vesicular and eosinophilic with irregular chromatin clumps and mitotic activity can be brisk, sometimes with atypical mitoses. These tumors have a mitotic rate of 9-10 per high-power field with a high KI67 labeling index and are frequently positive for p53. They also frequently associate with lymphatic and vascular invasion, in comparison with the well-differentiated proximal ECL carcinoid tumors.

G-cell hyperplasia with increased numbers of G-cells, numerous uniformly distributed in the lower and middle third of the antral glands affects patients with achlorhydria. Longstanding diffuse antral G-cell hyperplasia may progress to numerous small micronodular G-cell clusters and can eventually give rise to G-cell carcinoids (gastrinomas).

A number of carcinoid tumors, many of which are **gastrinomas**, develop in the proximal small intestine. Gastrinomas cannot be differentiated from other functional non-functional carcinoid tumors based solely on their histology. Immunohistochemical staining is required to make this diagnosis. These tumors tend to consist of small, uniform appearing cells, typically arranged in ribbons and trabecular, with vascular pseudorosettes. Most gastrinomas also produce other polypeptides in addition to the gastrin.

**Somatostatinomas** demonstrate mixed architectural patterns with architectural patterns with areas of insular, trabecular, glandular or acinar differentiation similar to those seen

in other endocrine tumors. A feature that distinguishes them from other gastrointestinal carcinoid tumors is the presence of psammoma bodies and a striking glandular appearance that makes them mimic carcinomas. However, in contrast to most carcinomas, somatostatin producing carcinoid tumors consist of uniform cells with few mitoses.

**Gangliocytic paragangliomas** are distinctive neoplasms that contain a mixture of spindle cells, epithelial cells and ganglion cells. The spindle cells often are a major component and are of unknown origin. They form compact fascicles that may envelop the nerves and axons and are positive for S100. The epithelial cells are larger with eosinophilic cytoplasm and contain uniform ovoid nuclei. The cells are arranged in ribbons, solid nests or in pseudo glandular structures. Ganglion cells are scattered singly or aggregated into clusters. Because these lesions typically arise at the ampulla ovata, the various components may mingle with the smooth muscle fibers in pancreatic ducts in this region.

**Mid-gut EC cell** serotonin-producing carcinoids consist of characteristic rounded nests of closely packed tumor cells, often with peripheral palisading. In another pattern, the solid nests associate with rosette-like or glandular structures. These are often called mixed insular or glandular type and may have a more favorable prognosis than the more nested carcinoid tumors. Most of the carcinoid tumors have a indistinct cytoplasm, indistinct cell borders and a little or no cellular pleomorphism or mitotic activity. Most mid-gut carcinoids are multi hormonal. When these tumors invade the muscularis propria, they insinuate themselves between the muscle fibers, spreading the muscle fibers apart rather than destroying them. A prominent desmoplastic response may lead to thickening of the bowel wall and fibrosis that extends into the mesentery. Concentric elastic vascular sclerosis frequently affects these large mesenteric vessels and these proliferations can obliterate the vascular lumens, leading to ischemia. The elastosis and fibrosis are not confined to the vessels, but may also surround tumor cell nests, resulting in extensive matting of involved tissues and lymph nodes, sometimes producing fibrous adhesions.

Classical **appendiceal carcinoids** resemble their ileal counterparts. Approximately two-thirds of cases extend to the peritoneal surface. As is the case in all carcinoid tumors, retraction artifact of fixed tissues often creates the false impression of lymphatic invasion. However, true lymphatic invasion occurs as demonstrated by finding lymphatic endothelial cells lining spaces surrounding tumor cells. Perineural invasion also occurs. Appendiceal tumors are unique in that they contain S100 positive sustentacular cells surrounding the tumor cell nests. This suggests the tumors arise from subepithelial neuroendocrine complexes rather than from intraepithelial endocrine cells.

One variant is the so-called tubular carcinoid, which consists of small obvious tubules, but not containing inspissated mucin. The nuclei are central, round or oval and have well-defined nuclear membranes. These tumors are often positive for chromogranin, glucagon, serotonin and IGA. They can easily be misinterpreted as metastatic adenocarcinoma.

Another tumor that arises in the appendix is the adenocarcinoid tumor. It is discussed later.

The histological features of large **intestinal EC carcinoid** tumors resemble small intestinal or appendiceal carcinoid tumors. However, these hindgut lesions exhibit moderate atypia and a high mitotic rate. Therefore they tend to behave more aggressively than the average mid-gut carcinoid tumor. The use of chromogranin stains to establish the diagnosis of a carcinoid tumor in the colon and rectum is often disappointing, since these results are frequently negative. We use synaptophysin staining regularly to demonstrate endocrine cell lesions in the GI tract.

### **Prognosis and treatment**

Carcinoid tumors are potentially malignant and identifying those that behave aggressively can be quite difficult, since the presence of local invasion in these slow-growing tumors does not have the same prognostic implication that it does in adenocarcinomas. The histological features alone usually do not allow one to predict malignancy. The distinction between a benign and malignant tumor traditionally relies on the presence or absence of metastases. However, an elevated mitotic rate often associates with a worse prognosis. When a tumor invades beyond the mucosa or metastatic spread is present, the lesion is considered to be potentially aggressive. If the lesion remains confined to the mucosa or submucosa that shows vascular invasion, or is larger than 1 cm, it is considered to be of **uncertain malignant potential**. Treatment usually consists of radical surgical excision of the tumor. Exceptions are gastric Type 1 and Type 2 lesions and rectal carcinoids that are managed by local excision. In general, the five-year survival is excellent for appendiceal carcinoids (86%) and rectal carcinoids where small intestinal, gastric and colonic carcinoids have five-year survival rates of 21-55%, 6-49% and 42%, respectively.

In the stomach, if the tumors are larger than 1 cm or more than 3 lesions are present, local excision of the fundic lesions and antrectomy are recommended. Antrectomy removes the sources of the hypergastrinemia that drives the tumor growth. In Type 2 ECL cell carcinoids clinical prognosis is usually determined by the presence of pancreatic or duodenal gastrinomas rather than by the ECL carcinoids. Nevertheless, some aggressive ECL tumors can be fatal. Type 3 ECL carcinoids measuring >1 cm usually require surgical resection even if they are well differentiated.

Approximately 25% of duodenal carcinoid tumors metastasize. Features associated with metastasis include extension to the muscularis propria; a maximum diameter of >2 cm; and the presence of mitotic figures. Gastrinomas, somatostatinomas and EC cell tumors that invade beyond the submucosa or those that develop lymph node or distant metastases behave aggressively. The liver is the most common metastatic site, followed by the regional lymph nodes and bones with patients with somatostatinoma. The high incidence of malignancy in somatostatinomas parallels that seen in glucagonomas and gastrinomas.

Gastrinomas that develop in the setting of ZES behave more aggressively than nonfunctional gastrinomas in are much more likely to develop metastases and be deeply infiltrative. Pancreatic gastrinomas behave more aggressively than duodenal gastrinomas. The rate of metastases of duodenal gastrinomas is 5% versus 52% in patients with pancreatic primary tumors. The ten-year survival rate of patients with duodenal gastrinomas is 59% compared with 9% for those with pancreatic gastrinomas. Gangliocytic paragangliomas usually behave in a benign manner, although occasionally they metastasize.

Jejunioileal carcinoids are potentially aggressive if they deeply invade the bowel wall or if there are metastases. By these criteria, up to 90% of jejunioileal carcinoids can be considered to be aggressive. Up to 35% of small intestinal carcinoid tumors metastasize. The metastases first involve the mesenteric lymph nodes and then the liver. Jejunioileal carcinoids have a 21% mortality rate, compared with 6% for gastric, 3% for rectal and 4% for duodenal carcinoids. The overall five- and ten-year survival rates for patients with jejunioileal endocrine tumors are 60% and 43% respectively. Patients without liver metastases have 5 and 10-year survival rates of 72% and 60% respectively, compared with 35% and 15% for those with liver metastases.

Appendiceal and colonic carcinoid tumors can be treated by local excision if they are found at an early stage (2 cm or less in maximum diameter). Although appendiceal carcinoid tumors often extend to the peritoneal surface, they do not behave aggressively as judged by the infrequent occurrence of lymph node or distant metastases. Tumors that are >2 cm in maximum diameter or invade the mesoappendix will have metastases or aggressive lesions. If the tumors arise at the base of the appendix and involve the resection margins, or the cecum, the prognosis is more unfavorable and requires partial resection of the cecum. The frequency of metastases ranges from 1.4 to 27% and distant metastases may occur. The five-year survival of patients with appendiceal carcinoid tumors is 94% for those with localized disease, 85% for regional disease and 34% for distant metastatic disease. In contrast, goblet cell carcinoids behave more aggressively than the usual carcinoids that are not as malignant as adenocarcinomas and tubular carcinoids are clinically benign.

Colonic EC cell carcinoids are often malignant with local spread occurring in up to 44% of patients and distant metastases in 38%. The five-year survival rate is 25-42% and the ten-year survival rate is 10%. Large colonic carcinoid tumors should be treated aggressively with standard colonic resection. These tumors metastasize to lymph nodes, liver, mesentery peritoneum, pancreas, ureters, ovaries, omentum and sometimes, other organs.

Rectal carcinoids are malignant in approximately 14% of cases. Features used to diagnose a malignant tumor include tumors measuring >2 cm in greatest diameter, invasion of the muscularis propria, atypical histological features and more than 2 mitoses to 10 high-power field, as well as the presence of aneuploidy.

The principal treatment for rectal carcinoid tumors is surgery. Tumors measuring <2 cm in diameter are quite suitable for local resection, whereas radical operations are required for larger lesions. If the tumor displays atypical histological patterns, a radical operation should be considered, even if the tumor measures <2 cm. Total removal with clear margins is essential to limit local recurrence in these tumors measuring <2 cm.

## ADENOCARCINOID

Adenocarcinoid tumors contain multiple proliferating epithelial cell types, including mucinous cells, endocrine cells and Paneth cells. Both poorly formed mucin vacuoles and endocrine granules can be present in the same cell. In a minority of lesions, the endocrine cell component is so prominent that the tumor resembles a conventional carcinoid tumor. In other tumors an inconspicuous endocrine component is detectable only after the use of special stains. In this situation, the tumor histologically resembles a signet ring cell carcinoma. Mucin or CEA stains highlight the goblet cells. Mucin also highlights the extracellular mucinous pools. Immunohistochemically, the endocrine cell component is positive for chromogranin A, synaptophysin, serotonin, glucagon, somatostatin, and/or pancreatic polypeptide. The goblet cells are immunoreactive for CEA. The mucosa is typically spared except in its lower portion where the tumor contacts the crypt bases. Mitotic figures are infrequent and there is virtually no cellular atypia. These tumors tend to infiltrate all layers of the intestinal wall to the serosa in the manner resembling typical carcinoid tumors.

## SMALL CELL CARCINOMAS

Small cell carcinomas are rare gastrointestinal tumors that are much more prevalent in Japan than in the United States. This is generally a tumor of older adults aged 38-74 with a mean age of 64-66 years and a predilection for development in men.

Patients with small cell carcinomas tend to present with crampy abdominal pain, malaise, weight loss, fever, diarrhea and rectal bleeding. In most patients the symptom duration is short, being only several weeks in duration. At the time of surgery, almost all of the patients have metastases to the regional lymph nodes and liver. The patients may also have symptoms secondary to the presence of a mass lesion. These tumors behave aggressively and often present with paraneoplastic syndromes that manifest as inappropriate antidiuretic hormone, hypercalcemia or watery diarrhea.

The gross features of small cell carcinomas are variable and nonspecific. Nothing distinguishes them from ordinary adenocarcinomas. They arise in the gut from the esophagus to the rectum. The tumors tend to be deeply infiltrative. Metastases affect the lymph nodes, liver, peritoneum and lungs.

Histologically, small cell carcinomas in all gastrointestinal sites resemble small cell carcinomas of the lung. This highly malignant epithelial neoplasm consists of cells that by ordinary histological examination appear undifferentiated. The use of special techniques allows one to show the features in neuroendocrine differentiation. Squamous

or glandular differentiation may also be present. The tumor contains sheets of densely packed dark, small, oval, spindled or fusiform shaped anaplastic cells with a dark, hyperchromatic nuclei and dispersed stippled chromatin. The nuclei are approximately twice the diameter of mature lymphocytes. Focal necrosis and high mitotic rates are common. The cell size may also be intermediate or large. These patterns recapitulate the small, intermediate and large cell variance of pulmonary small cell carcinomas. The tumors may also contain large mononucleated and multinucleated tumor cells with angulated, intensely hyperchromatic nuclei. Neuroendocrine-like trabecular rosettes may also be seen. The mitotic rate is high, ranging from 10 to 90 mitoses per ten high-power field. Vascular invasion is seen in the majority of cases. Cytokeratin stains may show punctate perinuclear cytoplasmic reactivity. Immunostaining with antibodies to chromogranin are often disappointing, but synaptophysin staining is strongly positive.

The overall survival is usually <2 years following the diagnosis because approximately 75% of affected patients with metastatic disease at the time of diagnosis. These aggressive tumors have a propensity for invasion and early metastasis to the regional lymph nodes. Even after aggressive treatment, patients die between two and twelve months after diagnosis. There is a significant difference in survival between patients with limited stage disease (defined as tumor-confined to the bowel wall) and those with more extensive disease.

#### OTHER TYPES OF NEUROENDOCRINE TUMORS

**Large cell endocrine carcinoma** is a malignant neoplasm consisting of large cells with an organoid nesting trabecular rosette-like and palisading pattern that suggests endocrine differentiation. The endocrine differentiation can be confirmed by immunohistochemical or ultrastructural examination. In contrast to small cell carcinomas, the cytoplasm is much more abundant, the nuclei are more vesicular and nucleoli are present. These lesions are rare.

**Mixed exocrine/endocrine tumors** are those tumors in which neoplastic endocrine cells constitute >30% of the entire tumor cell population. These lesions generally are classified as adenocarcinomas with focal neuroendocrine differentiation rather than as neuroendocrine tumors.

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