

**Pancreatic Neuroendocrine Tumors**

Tumors of the neuroendocrine system are typically classified into two distinct categories: carcinoids or pancreatic neuroendocrine tumors. Pancreatic neuroendocrine tumors form in the endocrine (hormone-producing) tissues of the pancreas and are also sometimes known as pancreatic islet cell tumors.<sup>1,2</sup>

Pancreatic neuroendocrine tumors are called "functioning" if they produce hormones that result in clinical symptoms associated with excessive hormone release or "nonfunctioning" if they do not. Most functioning tumors are benign, while more than 50 percent of nonfunctioning tumors are likely to be malignant.<sup>1,3</sup> Nonfunctioning pancreatic neuroendocrine tumors produce clinical symptoms from the primary tumor bulk or from metastatic dissemination.<sup>4</sup> Because nonfunctioning tumors do not produce symptom inducing hormones, they are often advanced before they are discovered.<sup>3</sup>

Pancreatic neuroendocrine tumors are different from exocrine tumors of the pancreas (pancreatic adenocarcinoma), which account for about 95 percent of all pancreatic cancers.<sup>5</sup> Pancreatic neuroendocrine tumors are slow growing tumors<sup>3</sup> that are fairly rare and are reported in two to four people per million annually worldwide<sup>6,7</sup> and account for approximately 22-28 percent of all neuroendocrine tumors.<sup>8,9</sup> The incidence of pancreatic neuroendocrine tumors appears to be rising, due in part to heightened awareness of the disease, improved diagnostic techniques and an increased rate of incidental diagnoses during evaluations for other conditions.<sup>10,11</sup> For patients with pancreatic neuroendocrine tumors that have metastasized, prognosis is poor, with a survival of only 1-3 years,<sup>12</sup> similar to that seen with metastatic breast cancer or metastatic colon cancer.<sup>13,14</sup>

**Pancreatic Neuroendocrine Tumors Subtypes**

There are several subtypes of pancreatic neuroendocrine tumors. Each may have distinct characteristics and is named according to the type of hormone-making cell of origin.<sup>3,15</sup>

- **Insulinomas** originate from cells that make insulin. The tumor makes too much insulin and causes the body to store sugar instead of burning the sugar for energy. This causes too little sugar in the blood, commonly called hypoglycemia.<sup>1</sup>
- **Glucagonomas** originate from cells that make glucagon. The tumor makes too much glucagon and causes too much sugar in the blood, a condition called hyperglycemia.<sup>1</sup>
- **Gastrinomas** originate from cells that make gastrin. The tumor makes large amounts of gastrin, which causes too much acid to be made in the stomach. Ulcers may develop as a result of too much stomach acid.<sup>1</sup>
- **Rare islet cell tumors:**<sup>1</sup>
  - **Somatostatinomas** originate from cells that make somatostatin. Ninety percent are malignant, and are associated with adult onset diabetes.<sup>15</sup>
  - **VIPomas** (Verner-Morrison Syndrome) originate from cells that make vasoactive intestinal peptide (VIP), characterized by watery diarrhea, hypokalemia (low levels of potassium in the blood), and achlorhydria (lack of hydrochloric acid in the digestive juices) (WDHA).<sup>15, 16,17</sup>
  - **Pancreatic polypeptidomas**<sup>1</sup> originate from pancreatic polypeptide cells in the endocrine pancreas. The function of pancreatic polypeptide is to regulate secretion activities (endocrine and exocrine), and has effects on hepatic glycogen levels and gastrointestinal secretions.

**Symptoms**

- Symptoms associated with functioning pancreatic neuroendocrine tumors are often caused by the hormone the tumor is producing. For example, an insulinoma may produce too much insulin, leading to very low blood sugar levels.<sup>18</sup>
- Nonfunctioning tumors usually present because of their size or metastatic spread and resultant clinical symptoms.<sup>19</sup>
- Symptoms of both functioning and nonfunctioning tumors may include pain in the abdomen, diarrhea, stomach pain, a tired feeling all the time, fainting, weight loss, or weight gain without eating too much.<sup>1,18</sup>

## Diagnosis

If symptoms exist, blood and urine tests are used to determine if the amounts of hormones in the body are normal. Other tests may include x-rays and special scans.<sup>1</sup>

## Treatment

Current treatment options for pancreatic neuroendocrine tumors are limited:

- Surgery is the most common treatment and currently the only curative option.<sup>15</sup> The doctor may take out the tumor and most or part of the pancreas. Sometimes the stomach is partially removed (gastrectomy) because of ulcers. Lymph nodes in the area may also be removed.<sup>1</sup>
- Combination chemotherapy may provide effective palliation (treat partially, but not cure completely) as well as increased survival in selected patients.<sup>4</sup>
- Hormone therapy uses hormones (somatostatin analogues) to relieve symptoms caused by the tumor by blocking activity of hormones.<sup>1</sup>
- Hepatic arterial occlusion or embolization uses drugs or other agents to reduce or block the flow of blood to parts of the liver in order to specifically deliver local chemotherapy to treat metastases in the liver.<sup>1</sup>
  - It is common for pancreatic neuroendocrine tumors to metastasize to the liver.<sup>11</sup>
- With the exception of pain relief from bone metastases, radiation therapy has a limited role in this disease.<sup>4</sup>
- Two targeted therapies are approved for the treatment of advanced pancreatic NET<sup>20,21</sup> and have the potential to change the treatment paradigm for the disease after years of limited therapeutic options.<sup>22,23,24,25</sup>

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