

# Biochemical prognostic indicators for pancreatic neuroendocrine tumors and small bowel neuroendocrine tumors

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**Abstract:** Pancreatic neuroendocrine tumors (PNETs) and small bowel neuroendocrine tumors (SBNETs) are rare tumors that are frequently diagnosed late in the course of the disease. Several biomarkers have been proposed in the literature as prognostic factors for patients with these tumors. This article discusses a recent publication in *Annals of Surgical Oncology* from the University of Iowa analyzing the effect of different biomarkers on survival in patients with PNETs and SBNETs.

**Keywords:** Pancreatic neuroendocrine tumors (PNETs); small bowel neuroendocrine tumors (SBNETs); pancreastatin; chromogranin A (CgA); neurokinin A; 5-hydroxyindoleacetic acid (5-HIAA); serotonin; neuron specific enolase; pancreatic polypeptide

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Pancreatic neuroendocrine tumors (PNETs) comprise 3-5% of pancreatic malignancies and have a better prognosis than pancreatic exocrine tumors (1). Approximately 1,000 are diagnosed per year in the United States (1). Significant prognostic factors include tumor grade, tumor size, nodal status, presence of metastatic disease, Ki-67 protein index, and neurovascular invasion. Predicting prognosis can be difficult as some tumors follow an indolent course, while others are more aggressive. Common tumor markers that facilitate the diagnosis and follow-up of these patients include chromogranin A (CgA), pancreatic polypeptide, and the specific hormone over-secreted in functional PNETs.

Similar to PNETs, small bowel neuroendocrine tumors (SBNETs) are frequently diagnosed later in the course of the disease since many patients remain asymptomatic until they develop signs of bleeding, obstruction, mesenteric ischemia, or carcinoid syndrome. Biochemical markers that may be used for the diagnosis and follow-up of patients with SBNETs include CgA, urinary 5-hydroxyindoleacetic acid (5-HIAA), pancreatic polypeptide, neuron specific enolase, and neurokinin A.

Recently, investigators at the University of Iowa evaluated the prognostic value of biochemical markers in patients with

SBNETs and PNETs (2). The charts of 98 patients with SBNETs and 78 patients with PNETs were retrospectively reviewed. Preoperative and postoperative values of serum neurokinin A, CgA, serotonin, and pancreastatin were analyzed to determine the effect on progression-free survival (PFS) and overall survival. When compared to patients with PNETs, patients with SBNETs in this study were older, more likely to be male, more likely to have node positive or metastatic disease, had a lower tumor grade, and had a shorter PFS.

The authors found no correlation between neurokinin A and PFS or overall survival for patients with SBNETs and PNETs on univariate analysis. Neurokinin A, a member of the tachykinin family, is frequently elevated in patients with midgut neuroendocrine tumors. Multiple institutions have shown that persistently elevated levels of neurokinin A in patients with neuroendocrine tumors are associated with worse survival (3,4). There is also data suggesting that neurokinin A may be helpful with determining a response to treatment for patients with midgut neuroendocrine tumors (4). The reliability of neurokinin A as a prognostic factor for SBNETs requires further investigation.

The researchers at the University of Iowa found that

preoperative serum serotonin was significantly associated with PFS, but not overall survival for patients with SBNETs. Plasma serotonin can be a useful marker for patients with SBNETs, but obtaining a consistent assay for serotonin in the blood is challenging, and is only performed at a few institutions (5). Instead, the breakdown product of serotonin, 5-HIAA, can reliably be obtained from a 24-hour urine collection. Prior to having levels checked, patients must refrain from certain foods (plums, pineapples, bananas, eggplants, tomatoes, avocados and walnuts) for 3 days prior to the test, and they must discontinue medications that elevate levels of serotonin (6). Urinary 5-HIAA levels have been tightly linked to the presence of carcinoid syndrome, and may be useful when following patients with advanced disease (7). Although some of the literature has suggested urinary 5-HIAA may be a potential prognostic factor for patients with SBNETs, other studies have not confirmed urinary 5-HIAA as a consistently reliable prognostic factor (6).

CgA, a glycoprotein expressed in most neuroendocrine tumors, first emerged as a potential marker in 1984 when the first immunoassay was developed (8). Thought to be one of the most reliable and general serum markers, CgA is frequently elevated in patients with SBNETs and PNETs (6). The sensitivity and specificity of CgA ranges between 70% and 100% depending on the extent of disease (7). The investigators at Iowa found that preoperative serum CgA was associated with overall survival but not PFS for patients with SBNETs, and had no correlation with survival in patients with PNETs. The reason for this result is unclear, since several other centers have demonstrated that elevated CgA levels are associated with degree of tumor burden and prognosis in patients with neuroendocrine tumors (9-12). The authors in Iowa have postulated that possibly some of their patients had falsely elevated preoperative CgA levels. For instance, CgA levels may be falsely elevated in pregnancy, Parkinson disease, untreated hypertension, steroid treatment or glucocorticoid excess, chronic atrophic gastritis, renal failure, and liver failure (6,7). In addition, because proton pump inhibitors may also alter CgA levels, these medications must be discontinued 2 weeks prior to checking the plasma CgA levels (7). Furthermore, somatostatin analogues may affect the level of CgA, and levels should be drawn at the same consistent time around injection.

While CgA levels are valuable for the majority of patients with PNETs, this marker is not always helpful for patients with gastrinoma. Clinicians need to be aware that CgA is almost always elevated in gastrinoma, since chronic

elevation of gastrin provokes hyperplasia of neuroendocrine cells in the stomach (12). In fact, some patients who underwent gastrectomy without resection of the primary tumor achieved normal CgA levels after surgery, indicating that the gastrinoma itself may not release large amounts of CgA (13). Moreover, CgA is frequently not elevated in patients with insulinoma, and should not be used to follow these patients (14). The investigators in Iowa did not report how many patients with PNETs had gastrinomas or insulinomas, and this may be another reason why CgA levels were not significant prognostic factors for patients with PNETs.

Pancreastatin is a post-translational fragment of CgA involved with insulin and glucose metabolism. Levels may be elevated in as many as 81% of SBNET patients (15). In 2010, a new assay was developed to measure pancreastatin with little cross-reactivity to CgA (16,17). Since that time, this marker has emerged as a potential valuable tool for the diagnosis and treatment of patients with neuroendocrine tumors (15,16). The investigators in Iowa concluded that higher preoperative pancreastatin levels predicted a worse PFS and overall survival for patients with PNETs, and a worse PFS for patients with SBNETs (insufficient events to analyze overall survival for patients with SBNETs). This effect was independent of age, presence of nodal disease, or metastatic disease. A study from Great Britain also demonstrated the prognostic value of pancreastatin in neuroendocrine tumors (18). However, there are mixed data in the literature whether CgA is superior to pancreastatin in terms of a reliable tumor marker in patients with SBNETs and PNETs (16,19).

Clinicians should be aware that patients must fast 10-12 hours before checking pancreastatin levels. Unlike CgA, proton pump inhibitors do not interfere with pancreastatin levels (20). However, any medication that interferes with insulin will affect the levels, since pancreastatin is involved with glucose homeostasis. Moreover, the role of pancreastatin in patients with insulinomas is unclear.

Other biochemical markers that were not investigated in Iowa include neuron specific enolase and pancreatic polypeptide. Neuron specific enolase is a tumor marker that may be elevated in as many as 38% of patients with neuroendocrine tumors (9). This marker is thought to be unrelated to the secretory activity of SBNETs, and may be helpful in some patients (7). However, CgA has been found to be a more sensitive marker than neuron specific enolase (9). Pancreatic polypeptide, a product of the normal pancreas, is a nonspecific marker that may be elevated in

patients with PNETs and SBNETs (21). This marker can be a good alternative, especially when CgA levels are normal.

Several biomarkers are available for patients with neuroendocrine tumors. To avoid excessive costs in an ever-growing healthcare system, clinicians should be cognizant of the true benefits and dependability of each marker. CgA is not elevated in all patients, and other markers such as pancreastatin and urinary 5-HIAA may provide valuable prognostic information depending on the specific disease process. It is imperative that clinicians recognize that SBNETs and PNETs represent two distinct disease processes, and the biochemical marker produced is dependent on the primary tumor. Likewise, future analyses regarding outcomes for patients with PNETs and SBNETS should be performed separately. In general, CgA is the most reliable marker for both PNETs and SBNETS according to guidelines provided by the North American Neuroendocrine Tumor Society (NANETS), the European Neuroendocrine Tumor Society (ENETS) and the National Comprehensive Cancer Network (NCCN). The role of other biomarkers such as pancreastatin in patients with neuroendocrine tumors is unclear, and future research is needed to determine which markers provide the best diagnostic and prognostic information.

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