Management of Pancreatic Endocrine Cancer
Considerations for Managed Care Decision Makers

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INTRODUCTION
Pancreatic neuroendocrine tumors (PNETs) are a group of rare neoplasms that arise from the hormone-producing neuroendocrine system of the gut. Because they are derived from cells that produce hormones that typically regulate the function of the gastrointestinal tract, they can sometimes secrete a variety of peptide hormones. These overproduced peptide hormones may include insulin, gastrin, glucagon and vasoactive intestinal peptide (VIP), resulting in myriad clinical syndromes. Modern data suggest that up to 75 percent of PNETs are nonfunctioning; that is, they are not associated with a hormone oversecretion syndrome.

Although this group of cancers is rare, the indolent nature of this family of malignancies and the long survival of patients stricken with this disease make it an important class of diseases for the managed care community.

EPIDEMIOLOGY
Historical perception is that pancreatic endocrine cancer is a rare disorder, but this is a family of tumors that has been increasing in frequency in recent decades. An analysis of the Surveillance, Epidemiology and End Results Database shows the historical estimated annual incidence is less than one case per 100,000. Some recent analyses show rates have increased up to 2.2 per 100,000. There is a preponderance of males to females (2.6 to 1.8). More aggressive radiologic imaging behavior by providers may be contributing to this increase. In other words, the tumor was present but was asymptomatic and growing so slowly as to lie undiscovered in the pancreas for a long time.

Autopsy studies show a strikingly different picture compared to the clinical trials, with rates around 10 percent. Hence there are many people that die of other causes who never knew they had a PNET. Interestingly, 19 percent of all pancreatic cancer discovered incidentally on computed tomography (CT) scans done for other reasons are PNETs. This statistic confirms the large number of “silent tumors” in the general population.

ADDITIONAL CLINICAL CONSIDERATIONS
Perhaps more importantly, PNETs are associated with many other significant tumors such as cancers of the ovary, breast, bladder, prostate and esophagus. So when a PNET is
discovered, it should be followed by a diligent search for other malignancies. The PNETs may occur alone but they also may be part of a genetic syndrome such as MEN1, von Hippel-Lindau disease, neurofibromatosis-1 or tuberous sclerosis, as these are syndromes associated with particular genetic abnormalities that predispose the patient to other cancers.

**TUMOR CLASSIFICATION AND HISTOPATHOLOGY**

These tumors typically present with the symptoms of hormone hypersecretion or as a result of the mass effect of the primary cancer. Clinically, therefore, they are separated into “functional” or “nonfunctioning” depending on the presence of the syndrome of inappropriate hormone hypersecretion.

Because they are heterogeneous and rare, designing a prognostic stratification tool has been quite a challenge. The presence or absence of hypersecretion does not provide prognostic information. These tumors are divided pathologically into poorly differentiated or low-grade tumors. While there are differences in terminology and grading for these tumors arising at different sites, all commonly used classification systems reflect a basic separation between more indolent, well-differentiated tumors and far more aggressive, poorly differentiated types that behave clinically more like small-cell carcinoma of the lung.

**DIAGNOSIS AND MANAGEMENT**

The initial steps involved in the management of PNETs are based upon surgical resection of the primary tumor. Optimal management includes assessment for biologically active hormones, localization of the primary tumor, determination of the involvement of the lymph nodes, search for metastatic disease, thorough family history looking for patterns of malignancy, histologic review of the tumor and, when applicable, search for other malignancy. The best management of a PNET is to surgically resect the lesion. However, only about 40 percent of tumors are resectable. Patients with unresectable disease have a wide variety of choices for therapy, ranging from somatostatin analogs to aggressive chemotherapy to peptide receptor radionuclide therapy.

**Symptoms and Diagnosis**

Patients present typically as asymptomatic but may present with diarrhea due to obstruction of the pancreatic duct resulting in the

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**References**

adenocarcinoma or a PNET. CT scanning of a PNET often produces an image that is hyperdense, giving an important clue prior to needle or endoscopic biopsy. The surgical resection should be carried out by a surgeon experienced in management of this type of tumor and should include a careful search for hidden other malignancy in the affected organs.

Management of Advanced Disease
Cytotoxic chemotherapy using streptozocin and doxorubicin or streptozocin and fluorouracil is an important component of managing advanced disease and had a response rate in the range of 45 to 69 percent. So despite their toxicity, these drugs remain in common use today.

Sunitinib and other tyrosine kinase inhibitors targeting vascular endothelial growth factor (VEGF) receptors are active in patients with advanced disease. These agents offer modest and consistent responses in multiple clinical trials. One large trial comparing sunitinib to placebo showed a progression-free survival of 11.4 months versus 5.5 months on placebo.

Everolimus is also active in this disease and when used in chemotherapy failures had a 9 percent response rate and disease control rate of 72 percent. There is also substantial evidence that PNETs, unlike carcinoid tumors, are sensitive to alkylating agents. The best use of these has yet to be defined but may include temozolomide alone or in combination.

Liver-Directed Therapy
Because the liver is often the initial and most serious site of advancing disease and because of the indolent nature of PNETs, this tumor is an ideal candidate for hepatic-related therapy. Therapeutic options include local ablation with surgical resection, radiofrequency ablation, cryotherapy, chemoembolization and radioembolization.

While the optimal sequence of many ablative, embolic and pharmacologic interventions remains unclear, it is certain that the first disruption of delivery of pancreatic digestive enzymes to the gut. Patients may also present with obstruction of the bile duct producing jaundice, or with pain in the upper abdomen simply related to the size and space-occupying nature of the tumor. Rarely, patients may present with gastric outlet obstruction.

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PNETs are a family of rare tumors that are often silent. Management involves surgical resection followed by monitoring for advanced disease. The liver is the most common site of advanced disease, and management includes a wide array of therapeutic options. The rarity of the tumor has not allowed development of clear guidelines on how to apply this myriad of therapies, so multidisciplinary teams with experience in PNets should manage those with advanced disease.