



CARING FOR CARCINOID FOUNDATION

Dedicated to discovering a cure for carcinoid cancer

Ask the Doctor March 2009

David C. Metz, M.D., Professor of Medicine: Associate Chief, GI Division for Clinical Affairs; Clinical Director, Hospital of the University of Pennsylvania; Co-Director, Motility-Physiology Program; Director, Acid-Peptic Program

1. Please clarify terminology; what are the different pancreatic endocrine tumors (PETs) and how are they classified? How do these PETs differ from neuroendocrine carcinoma of the pancreas?

Neuroendocrine tumors (NET) fall into two categories: Pancreatic endocrine tumors (PETs) and alimentary tract carcinoid tumors. Both subtypes can be functional or nonfunctional. Functional PETs include the gastrinoma, insulinoma, glucagonoma, VIPoma, etc. Pancreatic neuroendocrine carcinoma is a term used to describe a NET of the pancreas that tends to behave more aggressively than most NETs but is generally not distinguishable otherwise.

2. How frequently should a pancreatic endocrine tumor patient visit their oncologist and what tests should be performed? Should metastatic patients have more frequent follow-ups?

It all really depends on the stage of disease and rate of growth. Until this is known it is always a good idea to be seen frequently to permit serial testing to be done for this reason (often 3-6 monthly). I like to see my stable NET patients at least once yearly once I have had the opportunity to get to know how their tumors are behaving. I do feel patients with metastatic disease to the liver should be seen more frequently because they are potentially in a more aggressive phase of their diseases though this is very variable.

3. When do you use a whipple vs. other treatment options for pancreatic endocrine tumors?

PETs discovered at a stage when they are still potentially resectable (and curable) in the operating room should be referred for surgery by an experienced surgeon. Surgery may also be indicated to debulk larger metastatic tumors in the hopes of improving long term outcome though this is a controversial point. If the lesion is in the head of the pancreas this often requires a Whipple's resection (pancreaticoduodenectomy) in which the head of the pancreas and part of the duodenum are removed. The operation then requires reanastomosis (reconnection) of the bile duct and pancreatic duct which normally empty into the duodenum elsewhere along the GI tract as well as another anastomosis (connection) of the stomach to the small bowel. Occasionally pancreatic head lesions can be enucleated (preferred for insulinomas which are often benign) but this is not always possible. For lesions in the tail of the pancreas the usual operation is a distal pancreatectomy (often with a splenectomy as well). This is a less technically demanding operation that does not require multiple anastomoses but it cannot be done for lesions in the head of the pancreas. Patients should get vaccinated for encapsulated microorganisms before undergoing a distal pancreatectomy if there is time (the spleen is

important in generating a response to these infections). Finally, patients with Multiple Endocrine Neoplasia type I may not benefit from extensive surgery at presentation (as opposed to patients with sporadic – non-inherited PETs) and we usually try to avoid initial attempts at curative surgery in this group unless their PETs tumors are large.

4. Should pancreatic endocrine tumor patients take somatostatin analogs? Are there risks of dependency or dose escalation?

Somatostatin analogs are FDA approved for the VIPoma syndrome (one of the PETs), the carcinoid syndrome (one of the alimentary tract carcinoids) and acromegaly (a NET of the pituitary gland). These are all syndromes that result from overproduction of a peptide that can be suppressed by somatostatin. However, somatostatin analogs are also often used (off label, i.e., not FDA approved) for patients with metastatic disease in the hopes of reducing their rate of growth (as well as for gastrointestinal bleeding from varicose veins in people with portal hypertension from cirrhosis of the liver). The data on this antigrowth effect are not clear and their use is therefore controversial though many experts embrace this response because it is generally well tolerated and may be beneficial. Somatostatin therapy can cause gallstones and steatorrhea – excess fat in the stool. Tachyphylaxis (tolerance and loss of efficacy with time) is a theoretical concern with somatostatin therapy and dose escalation may be considered in individualized cases.

5. What are the diagnostic and prognostic indicators for PETs; what considerations do you take into account when determining the best treatment for a specific patient?

While many functional syndromes can be diagnosed based on peptide levels (sometimes with provocative blood tests), the best way to diagnose any NET is to obtain tissue at biopsy. Prognostic information can be gleaned based on patient factors (age, associated diseases) or tumor factors (histologic [i.e., under the microscope] appearance, spread, rate of growth, molecular studies of tumor tissue or blood markers) and response to therapy. However, no firm recommendations exist regarding how to best treat specific patients and therapy should be individualized.

6. When PETs metastasize to the liver; do the liver tumors behave more or less like the primary PET?

- If the PET was slow-growing, are the liver mets also likely to be slower growing?
- Do non-functioning PETs spawn liver mets which are different from liver mets spawned by functioning PETs?
- Also, are treatments successful against the PET likely to be successful against the liver NETs?

This is not very well studied so we cannot be sure about the answer to these questions. In general, I think liver metastases do behave in a similar way to the primary tumor. Rate of growth is probably similar though the rate of growth probably increases as the tumor bulk increases so widely metastatic tumors (which have likely been present for many years) probably grow more

rapidly as time goes on. Metastatic functional tumors probably are still functional. Occasionally very widespread tumors can start making a new product in addition to the initial one such as ACTH production after initially presenting as a gastrinoma. Treatments are generally directed against all sites of tumor (except for specific liver-directed approaches used in patients with large tumor bulk in the liver who may not be getting symptoms from other sites).

7. What are the major differences between islet cell tumors and carcinoid tumors?

The term islet cell tumor is synonymous with a pancreatic endocrine tumor (PET).

8. Is there a “carcinoid crisis” for islet cell patients: Can islet cell patients go into crisis with falling blood pressure?

The carcinoid crisis refers specifically to sudden release of vasoactive peptides from carcinoid syndrome-producing tumors. During surgery, PETs can release more peptide into the blood exacerbating the hormonal syndrome but usually these patients are blocked in the OR with somatostatin analogs to limit such effects.

9. What is the rationale behind combination therapies such as combining Xeloda, Avastin, and Oxaliplatin in a clinical trial?

The hope is that by combining therapies that act to kill tumor cells by different mechanisms at the same time may provide an augmented (more than additive) effect and a better outcome.

10. There is much recent advertising on the use of "Cyberknife" for surgery of inoperable tumors. Is this type of method being used for Pancreatic endocrine tumors or metastasis? Knowing each persons medical condition is different, when would it be appropriate and when should patients consider it as a treatment option?

I have no experience with this sort of surgical therapy for PETs though surgeons often combine various methods in trying to remove as much tumor as possible in the OR –resection, enucleation, radiofrequency ablation, etc. It is important that patients contemplating surgery for PETs (localized or metastatic) seek treatment with an experienced surgeon who may be able to use various modalities in the OR.

11. When do you recommend that pancreatic endocrine tumor patients consider peptide-receptor radionuclide therapy? Which do you recommend?

There was much excitement about Yttrium labeled somatostatin analogs for metastatic PETs. Unfortunately these therapies were not shown to be useful in clinical trials. We remain hopeful however that newer radionuclide therapies will be shown to be successful (especially gallium analogs).

12. What is the most promising new treatment in development for pancreatic endocrine tumor patients?

I remain hopeful that the new tyrosine kinase inhibitors and mTOR inhibitors will be shown to have efficacy for metastatic PETs.

13. My husband was recently diagnosed with a neuroendocrine tumor of the pancreas. It is approximately 1.5 X 1.4 cm and was discovered incidentally by an abdominal ultrasound. He is 30 years old & asymptomatic. The EUS with FNA showed the tumor to be synaptophysin and chromogranin positive, somatostatin, gastrin & insulin negative. We assumed this to be a non-functioning tumor. Initial chromogranin A levels were well within normal limits. I was wondering if you could tell me what outcomes/prognosis have been based on your experiences in dealing with these tumors. The EUS report states that the lesion is invading the splenic artery due to abutment. Does this necessarily mean that this is an invasive lesion or could it be labeled as "invasive" simply because it is lying next to the artery? I realize that invasive lesions are considered to be more malignant and that is why I ask.

This is a difficult question to answer without knowing all the details. At autopsy, 1% of individuals harbor small PETs so that would suggest that many of us have small lesions that pose no threat. However, all large tumors had to have started out as small ones. We have no clever ways of identifying which these would be. In the case of your husband's tumor, I am a little concerned about the fact that on EUS there is a suggestion of splenic vein involvement as that may imply a more aggressive tumor. It is important that your husband is being evaluated at a center that sees many such tumors so that his therapy can be appropriately individualized.