

Preoperative Evaluation in Pancreatic Cancer- How much is enough?

*Mark P. Callery, MD, FACS
Associate Professor of Surgery
Harvard Medical School
Chief, Division of General Surgery
Beth Israel Deaconess Medical Center
Boston, Massachusetts USA*

Pancreatic cancer is the fourth leading cause of cancer-related deaths in America for both men and women, and 30,500 new cases will occur annually. It represents 2% of all cancers, but 5% of all cancer deaths. In the last 70 years, the age-adjusted mortality rate has tripled in the USA, Japan and Europe, affecting all age groups and both sexes. Despite perceived advances in aggressive surgical and adjuvant therapies, the 5-year survival rate remains abysmal at 4% and has not changed in the past 2 decades. At the time of diagnosis, only 10-15% of tumors are resectable and aggressive pancreatectomy confers at most a 23% 5-year survival. The majority of patients are not eligible for surgical therapy due to advanced disease at the time of diagnosis and 5-year survival is rare. With median survivals limited to only months, patients and clinicians dealing with pancreatic cancer are justifiably desperate.

The clinical diagnosis of a symptomatic pancreatic cancer usually occurs too late. Although some fortunate few may present with limited disease obstructing their bile duct in the pancreatic head, over 85% of patients become symptomatic only after the tumor has become locally invasive or systemic. We as clinicians must streamline their clinical evaluation with two critical objectives in mind. First, since surgical resection remains our only potentially curative treatment, our evaluation must identify which patients are candidates. Second, and as importantly, our evaluation must identify non-candidates so that they may be spared the toll of a futile operation as they enter the final stage of their lives. To achieve these objectives, we invoke a comprehensive clinical exam, obtain serum tumor markers, and submit patients to a menu of today's state-of-the-art imaging modalities. But does every patient need every study? No. A preoperative evaluation can and should be streamlined.

Comprehensive Clinical Assessment

Unfortunately, patients typically experience non-specific symptoms of an insidious disease. Their cancer has usually taken hold before the anorexia, malaise, fatigue, weight loss and pain prompts them to seek medical care. Physical findings reflect the incurable disease sometimes to the extent of malignant ascites and wasting. As noted, obstructive jaundice is our earliest warning sign, and should always be investigated urgently. New onset diabetes, exocrine insufficiency, depression and venous thrombosis also can occur. A careful history may reveal smoking, obesity, a sedentary lifestyle, long-standing chronic pancreatitis, and even a hereditary predisposition. The primary physician correctly checks baseline laboratory values, a Chest X-Ray, and in most cases, a relatively basic abdominal CT Scan. The findings typically prompt a specific referral pattern. Obviously inoperable patients see a medical oncologist, potentially operable patients see a pancreatic surgeon, and jaundiced patients usually see an interventional endoscopist. At these entry points, today's technology is put to work.

Tumor Markers. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) can be elevated in the blood of patients with pancreatic cancer. Neither is specific for the disease, and neither accurately screens for early stage disease. CA 19-9 is the more reliable, with

some studies correlating elevated levels (>300 U/ml) with unresectability. Oncologists often track these tumor markers when evaluating disease progression or recurrence. For surgeons, these are inadequate determinants of resectability.

Imaging Studies. Stunning advances in pancreatic imaging over the past 20 years have increased our ability to evaluate pancreatic cancer. Today's imaging power enables us to establish the diagnosis, identify candidates for resection, plan our surgical approaches, and identify inoperable patients. What are our options?

1. *Computed tomography-* CT is our mainstay given its capacity to detect and locally stage pancreatic cancer. It is highly reliable, especially for demonstrating unresectable disease. It still has limitations (small metastases, peritoneal implants, malignant lymph nodes) despite its new power from helical scanning and three-dimensional digital reformatting.

2. *Ultrasonography-* Although non-invasive and inexpensive, transabdominal US is inadequate for this disease compared to CT.

3. *Magnetic Resonance Imaging-* The added cost and, for some patients, uncomfortable experience adds very little to what helical digital CT provides. MRI does have value, however, in non-invasive pancreatic and biliary duct imaging.

4. *Positron Emission Tomography-* Whether used alone, or combined with CT, FDG-PET studies have very limited utility in pancreatic cancer staging, and can be omitted.

Endoscopic Evaluations. As noted, many patients are initially triaged to interventional endoscopists, especially when jaundiced. At our center, the majority of patients undergo some type of endoscopic procedure, ranging from diagnostic to therapeutic to palliative. We abide by a multidisciplinary approach whenever possible.

1. *Endoscopic Retrograde Cholangiopancreatography-* Over 90% of patients with pancreatic cancer will have abnormal ERCP findings, although they are never entirely disease specific. With such diagnostic strengths come limitations. ERCP is invasive and highly operator-dependent. It carries a 5-10% risk of pancreatitis. In talented hands, ERCP is pivotal in expediting the diagnosis, relieving jaundice by stent placement, and establishing tissue diagnosis of cancer by brush cytology or forcep biopsy. Many disagree, however. Some claim that biliary stent placement preoperatively increases the risks of operation. All agree that false negative cytology is common. We have resected several early (and late) stage cancers based only on suspicious ERCP findings. Everything considered, I believe ERCP will remain a mainstay evaluation in pancreatic cancer because it's diagnostic and therapeutic value, as well as its favorable location in patient triage and referral patterns.

2. *Endoscopic Ultrasound-* When performed by an expert with state-of-the-art equipment, EUS is highly sensitive for detecting and staging pancreatic cancer, with special power in detecting lesions under 3cm. It is useful, but not necessary, in determining resectability when non-invasive helical CT is available. As will be discussed, it has real value when tissue must be obtained for diagnosis.

3. *Endoscopic Palliation Techniques-* Obstructive jaundice, duodenal obstruction and even pain can be successfully managed endoscopically. Biliary endoprotheses, luminal metal stents, and EUS-guided celiac plexus blocks are commonly used to help unresectable patients overcome these symptoms without a painful, futile operation.

Staging Laparoscopy. There are numerous studies available in hepatobiliary and pancreatic malignancies that prove SL is valuable and should be utilized. There are also studies to indicate that not every potentially resectable patient need undergo SL. Together with laparoscopic ultrasound, and for some, peritoneal cytology, SL accurately predicts tumor resectability, identifies occult metastases other studies (CT) cannot, and in the end, eliminates unnecessary laparotomy in up to 20% of patients thought to be resectable by conventional

imaging techniques. Some favor limited techniques just prior to resection, others extended techniques under separate anesthetic.

Practical Recommendations for Typical Clinical Scenarios

Given this brief review of what we can do to evaluate pancreatic cancer patients, we can consider how and why to streamline our evaluations. No recommendation is perfect for every patient, and many high-volume centers may offer different and effective strategies. In my experience, the following evaluation strategies “are enough” for these typical clinical scenarios.

I. Initial Evaluation for possible pancreatic cancer.

- *Comprehensive History and Physical Examination*
- *Chest X-Ray, Baseline Laboratory Survey*
- *Dual-Contrast thin cut Abdominal CT Scan* – This study may vary in quality across centers, but it is our best initial determinant of unresectability. Unfortunately, this is how most new patients will present.

II. Unresectable Pancreatic Cancer

- *Dual-Contrast thin cut Abdominal CT Scan*- Because we will use this study to disqualify patients from any attempt at resection, it must be of the highest quality. As noted, today’s highest resolution spiral scanners provide digital data, arterial and venous reformatting, and must be utilized. CT-Angiography criteria for tumor resectability include (a) Absence of non-contiguous, extrapancreatic disease, (b) patency of the superior mesenteric/splenic/portal vein confluence, and (c) no evidence of tumor extension/encasement to the superior mesenteric artery
- *Tissue Diagnosis*- There are many modalities to achieve this, and the choice should be for the least invasive. CT or US- guided percutaneous biopsy of an unresectable mass is least invasive. If necessary, EUS guided biopsy is reliable, and can be combined with endoscopic palliation.
- *ERCP and stenting*- Unresectable lesions causing biliary obstruction warrant permanent metal stent placement. Late duodenal obstruction can also be suitably palliated with endoscopic stenting.
- *Avoid Surgery whenever possible.*
- *Medical Oncology referral for palliative care.*

III. Resectable Pancreatic Cancer

1. **Preoperative Neoadjuvant Chemoradiation Therapy**- Today, many centers offer a preemptive systemic and locoregional treatment strategy before attempting resection in patients with resectable, and even marginally resectable tumors. This adds to a pre-operative evaluation.
 - *Dual-Contrast thin cut Abdominal CT Scan*- determines resectability.
 - *Tissue Diagnosis*- This is required to begin neoadjuvant therapy. Typically, EUS-guided fine needle aspiration biopsy is simple, reliable and acceptably invasive. Percutaneous biopsy is not advisable.
 - *ERCP and stenting*- Necessary for jaundiced patients before commencing neoadjuvant therapy. May also provide tissue diagnosis, eliminating need for EUS-guided FNA.

- *Staging Laparoscopy*- Because occult metastatic disease can be identified by SL in 10-20% of patients presumed resectable by CTA, we believe SL should be performed prior to commencing neoadjuvant therapy.
 - *Re-staging CT-Angiogram*- if still resectable, proceed to laparotomy.
2. **No Preoperative Therapy**- Most centers move directly to laparotomy when potentially resectable pancreatic cancers are discovered. The preoperative workup should be limited and prompt.
- *Dual-Contrast thin cut Abdominal CT Scan*- determines resectability. Digital reformatting CT-Angiography has eliminated any need for traditional angiography. The images can indicate arterial and venous clearance from tumor, and help the surgeon in planning the operative approach, especially in the presence of anomalous arterial anatomy, or need for venous resection.
 - *Tissue Diagnosis*- By any approach, either pre- or intraoperatively, there is no need or value of obtaining tissue diagnosis. This is not recommended.
 - *ERCP and stenting*- Not necessary preoperatively in most, but often unavoidable given patient triage and referral patterns. We favor stenting in significantly jaundiced patients before operation since scheduling realities and general patient malaise warrant symptom relief.
 - *Staging Laparoscopy*- We follow recommendations for subsets of pancreatic tumors when utilizing SL for presumed resectable disease. We routinely perform SL for larger tumors, especially in the body and tail of the pancreas, but omit SL for smaller periampullary lesions under 2cm or so. For some patients, unnecessary laparotomy will be avoided. This remains controversial despite compelling evidence of the value of selective SL.

IV. Suspected, but Unproven, Pancreatic Cancer

Given both the magnitude of surgery required for cure, and the lethality of a missed diagnosis, this is a daunting and more common clinical scenario. Earlier studies have been recently validated and indicate that patients can be helped with an aggressive surgical strategy. This is probably the clinical scenario where no extent of preoperative evaluation “is enough”. We are currently evaluating the impact of EUS in this scenario. Ultimately, once everything is considered, patients and surgeons will correctly select preemptive resection.

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