

This lecture is drawn from the continuing medical education program “Finding Hope: Prevention, Early Detection and Treatment of Pancreatic Cancer”, Nov, 2011. Robert P. Jury, MD

Cystic Neoplasms of the Pancreas: A multidisciplinary approach to the prevention and early detection of invasive pancreatic cancer.

Pancreatic cancer is known to be one of the most difficult malignant diseases we face today. While teams of dedicated scientists and caregivers are battling the disease on many fronts, still over 212,000 deaths occur every year throughout the world with more than 38,000 in the United States alone. Our current understanding of the genetic evolution of pancreatic cancer suggests that invasive pancreatic cancer develops from changes in genes within a cell that may begin as many as 21 years before cancer has the ability to spread and lead to death. Clearly, a large window of opportunity for intervention exists.

This is a lecture about prevention, early detection and most importantly, curable conditions that lead to invasive pancreatic cancer when left untreated. We will focus on pancreatic cysts that may lead to cancer, and are being discovered with increasing frequency on a daily basis.

Until recently, cysts of the pancreas were frequently ignored, under-recognized or simply called pseudocysts. Enlargement of the main pancreatic duct was commonly attributed to chronic pancreatitis or inflammation, even when patients never had history or reason to suspect pancreatitis. To add to the problem, terminology regarding cystic lesions was confusing and the association with cancer unknown.

With the widespread use of sophisticated x-rays, including over 50 million CT scans in the United States each year, the incidental discovery of cysts in the pancreas or enlarged pancreatic ducts in patients without symptoms provides us with the opportunity to intervene earlier, and more effectively treat or prevent pancreatic malignancy. Studies have shown that as many as 20% of patients who undergo MRI of the abdomen will be found to have some type of cyst in the pancreas. As you might expect, patients who are found to have any abnormality in the pancreas whatsoever, are frightened and need careful evaluation and counseling. While the incidental discovery of these potentially serious lesions can lead to lifesaving treatment, health care providers are now faced with difficult and complex decisions to direct patients to a safe and effective treatment or follow-up. Guidelines are needed, and final recommendations must consider the age and overall medical condition of the patient affected.

In this lecture we will review the common cystic growths of the pancreas and review current guidelines for care. In 2006, a working group of The International Association of Pancreatology led by Professor Masao Tanaka published the first international consensus guidelines that define and identify the malignant potential of intraductal papillary mucinous neoplasm or IPMN and mucinous cystic neoplasm. This landmark paper, now commonly referred to as the Sendai Guidelines, has provided a most important foundation for our understanding of these lesions, which are known to lead to invasive pancreatic cancer.

While it is beyond the scope of this lecture to thoroughly discuss all cystic lesions that may occur in the pancreas, we will focus on 4 of the most common and important types.

Pseudocysts of the pancreas are a common finding in patients with abdominal pain and a clinical history of pancreatitis. Pancreatitis is a disease characterized by inflammation of the pancreas and is commonly associated with alcohol use, gallstones, medications or a variety of other causes. While pancreatitis of any type can cause cysts or fluid filled areas in the pancreas, it is important to remember that cystic tumors of the pancreas can actually be the cause of pancreatitis, rather than the result.

Pancreatic pseudocyst is characterized by a thick wall of scar-like tissue. Cyst fluid is typically rich in digestive enzymes like amylase, which is normally made by the pancreas and characterized by the presence of chronic inflammatory cells. While previously assumed to account for 90% of pancreatic cysts, most pancreatic cysts discovered today actually represent cystic neoplasms or tumors which commonly include serous cystadenoma, intraductal papillary mucinous neoplasm and mucinous cystic neoplasm.

Serous cystic neoplasms account for more than 30% of neoplastic cysts of the pancreas. They occur most commonly in females (3:1) with a mean age of 62 years. These cysts are filled with a thin watery fluid. Serous cystadenoma is often referred to as microcystic adenoma due to its appearance as a cluster of small cysts forming a honeycomb like structure. Characteristic imaging findings include a central star-like scar with calcification in 30% of cases.

Cancer in serous cystic neoplasm is extremely rare. For that reason, serous cystadenoma is considered to be a benign disease. Indications for surgical removal include symptoms of abdominal pain, usually associated with lesions larger than 4 cm or 1 ½ inches, or inability to distinguish the lesion from other cysts which may have risk of leading to cancer.

Mucinous cystic neoplasm occurs almost exclusively in women (95%) with an average age of 53 years. These lesions account for nearly half of all primary cystic neoplasms and occur most often in the middle or left side of the pancreas. On imaging, these lesions are characterized by larger cyst compartments and do not communicate with the main pancreatic duct. Mucinous cystic neoplasms or tumors do have the potential to become malignant or cancerous with time.

Much like we know that polyps in the colon will progress to colon cancer after several years, the lining of these pancreatic cysts will show changes in which normal cells become more cancer-like until they progress to frank cancer with the potential to spread and threaten the life of the patient. Often we will see these changes side by side in a single cyst showing how cancer progresses. On CT scans or MRI, mucinous cystic neoplasms may demonstrate thick walls, solid components and peripheral eggshell-like calcifications, all of which suggest a greater likelihood of cancerous transformation.

While the incidence of “cancer” in mucinous cystic neoplasms has been estimated to reach 36% at diagnosis, more recent classifications show invasive carcinoma to be found in 6-20% of removed specimens. Lesions less than 3 cm which lack risk factors for malignancy like thick enhancing walls, mural nodules or peripheral calcifications, rarely demonstrate cancer. For that reason, a patient may be advised to simply follow a pancreatic cyst with repeated testing over several years rather than to undergo surgical removal of that portion of the pancreas containing the cyst. Nevertheless, all mucinous cystic neoplasm must be considered to harbor malignant potential and need to be surgically removed or followed with that in mind.

Intraductal papillary mucinous neoplasm or IPMN is a premalignant lesion of the pancreas representing about 25% of all cystic pancreatic neoplasms. The disease is most often discovered in the 6th to 7th decade of life and affects men slightly more often than women. The condition is characterized by enlargement of the main pancreatic duct that carries digestive juices and enzymes into the intestine. The main pancreatic duct or the feeding side branches can be affected by an abnormal lining that produces excessive amounts of thick mucus. While the mucus itself may contribute to symptoms of abdominal pain or poor digestion of fat in the diet, the most significant problem lies in the abnormal cells that line the duct and become cancerous with time. Like polyps in the large intestine, cancer can be prevented when treated appropriately at an early stage

Based on the x-ray appearance of IPMN, the disease is classified as one of three types: main duct IPMN, branch duct IPMN and mixed type, with involvement of both main pancreatic duct and its side branches. Branch duct IPMN is seen to be multifocal in 30% of cases, and is considered to have a more indolent course and lower incidence of malignancy than seen in patients with main duct involvement. When the main pancreatic duct is involved as evidenced by dilatation greater than 6mm, mural nodularity from papillary ingrowth or the visible extrusion of mucus from a dilated opening by endoscopy, the risk of malignancy at diagnosis ranges from 50-92%. Of those, approximately half will be limited to carcinoma-in-situ, which is virtually curable in all cases.

This well established risk has led to a general recommendation for surgical removal at the time of recognition for those patients deemed fit for surgery. In addition, patients with symptomatic IPMN or those with suspicious radiographic features as described earlier for mucinous cystic neoplasm are considered to be at high risk for malignancy

and warrant consideration of surgery. Symptoms of IPMN include abdominal pain, weight loss, pancreatitis and pancreatic insufficiency.

For the remainder of this discussion, we will focus on the challenges of clinical decision-making and the timing of surgery for patients with asymptomatic cysts in the pancreas that are found incidentally. While main duct IPMN normally warrants surgical resection due to the high risk of malignancy, the growing population of elderly individuals with other medical problems begs for the discovery of biomarkers or tests from the blood or cyst fluid to indicate change toward cancer. While the safety of major pancreatic surgery like the Whipple procedure has improved through both the regionalization of pancreatic surgery to high volume centers, and the assembly of dedicated teams of pancreatic specialists; the potential for death or complications of surgery need to be balanced against the risk of progression to advanced or fatal pancreatic cancer. Appropriate surgical treatment requires major surgery like the Whipple procedure or removal of the left half of the pancreas, sometimes including the spleen.

Laparoscopic pancreatectomy has proven to have a place in treatment and may be especially useful for lower risk lesions involving the body and tail of the pancreas. While minimally invasive approaches may speed recovery, the potential for complications such as pancreatic fistula and the cardiorespiratory impact of general anesthesia remains unchanged. While we strive to diagnose and treat potentially malignant disease when cure remains possible, we need to make every attempt to avoid the rigors of surgery for those patients who are unfit or at low risk for cancer.

Currently, evaluating risks for asymptomatic pancreatic cysts is generally based on the morphologic characteristics seen on imaging studies. Appropriate application of the Sendai guidelines requires high quality cross-sectional imaging by dual phase, thin-slice pancreas protocol CT or gadolinium enhanced MRI with MRCP. Dedicated radiologists communicating effectively with primary care physicians, gastroenterologists, and surgeons help to guide patients to appropriate treatment. Complimentary to the role of CT and MRI is that of endoscopic ultrasound or EUS providing additional imaging information as well as the opportunity to sample fluid for biochemical markers and cytologic analysis.

Along with gastroenterologists and surgeons skilled in EUS and ERCP, cytopathologists and molecular biologists play an increasingly important role in the management of pancreatic disease.

The analysis of cyst fluid has become a primary focus of translational research in an effort to differentiate benign from malignant disease. Fluid analyses including cytology, viscosity, extracellular mucin, CA19-9, CA15-3, CA17-4, amylase, and others have provided little to help differentiate benign from malignant disease. Examining cells from fluid under the microscope is often difficult due to contamination of normal stomach lining. To date, cyst fluid CEA levels >192 ng/ml and extracellular mucin are most accurate in differentiating mucinous lesions such as IPMN and mucinous cystic

neoplasm from serous cystadenoma and pseudocyst, helping clinicians and patients to consider treatment and surveillance options.

With extensive research and discovery of the genetic alterations commonly associated with pancreas cancer, the Pancreatic Cyst DNA Analysis Study known as the PANDA study looked at cyst fluid from 113 patients undergoing resection or aspiration of pancreatic cysts. In this study KRAS, a common mutation associated with pancreatic cancer was not found to be independently predictive of malignancy. However, when combined with other markers, the identification of mucinous lesions was possible. Even so, findings did not reliably allow for discrimination of malignant change. Most recently, Ryu and the colleagues at Hopkins have noted the predictive value of cyst fluid microRNA, miR-21 in distinguishing mucinous from non-mucinous pancreatic cysts. While their pilot study did not attempt to determine whether these microRNAs could distinguish invasive from non-invasive lesions, the study gives further promise to the biomarker discovery

Summarizing the current guidelines for the management of primary cystic neoplasms of the pancreas, the following take-home messages should be considered:

1. All patients with cystic neoplasms of the pancreas should be considered to be at risk for malignancy.
2. All patients with main duct IPMN should be CONSIDERED for surgical resection.
3. The differentiation between mucinous and non-mucinous lesions is often complex.
4. Guidelines for safe surveillance apply only to ASYMPTOMATIC individuals.
5. Risk factors for malignancy in asymptomatic patients with mucinous cystic lesions include:
 - a. Size greater than 3.0 cm
 - b. Mural nodules or other solid elements
 - c. Thick enhancing wall or septae
 - d. Peripheral calcifications
 - e. Atypical cellular features on fine needle aspiration biopsy

Patients without high risk features requiring surgery should be subject to surveillance. Options for follow-up include pancreas protocol CT, MRI with MRCP and endoscopic ultrasound. Given the likely need for multiple studies over years of follow-up, cumulative radiation exposure in younger patients should be avoided favoring MRI over CT. While endoscopic ultrasound is more invasive, the opportunity for cyst fluid analysis adds benefit. The value of cyst fluid analysis will undoubtedly increase as translational research provides new biomarkers to indicate malignant progression.

Surveillance guidelines for asymptomatic lesions are variable and somewhat inconsistent, as the natural history of mucinous neoplasms is not fully known. A conservative approach includes follow-up examination at 6-month intervals during the first 2 years after discovery. Annual examination is advised during the second two years to document at least 4 years of stability. All recommendations should consider patient

age, co-morbidity and the feasibility of surgical resection if progression to malignancy is suspected. Complex mathematical models have been created to assess quality of life measures and cost-effectiveness, comparing surgery to surveillance in different age groups. However there is no substitute for individualized care plans based on a thorough understanding of the disease and thoughtful consideration of the best interest of the patient involved.

The impact of appropriate management of cystic precursor lesions is demonstrated by 5-year survival rates of >90% for patients with non-invasive IPMN or mucinous cystic neoplasm compared to approximately 50% when invasive carcinoma is found. Effective management of patients with these and other pancreatic diseases requires a multidisciplinary approach. Teams of specialists with excellent communication and the support of knowledgeable Nurse Navigators have become increasingly important in assisting primary care physicians and their patients in dealing with this condition. Most importantly, we must focus on furthering our knowledge and improving awareness, as we remain determined and hopeful to beat this difficult disease.