Commentary

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This commentary serves to: (1) draw attention to the importance of the chapter by Professor Buechler's group; (2) reinforce the concept that identification and screening of patients with pancreatic cysts is a unique opportunity to prevent and cure pancreatic cancer through early detection and (3) review current management and anticipate future changes in management of these complex patients.

Pancreatic cancer is the deadliest cancer. Although the incidence of pancreatic cancer is only 45,000 cases per year, the mortality is substantial. The mortality from pancreatic cancer is on an upward trajectory to surpass the mortality from breast cancer in the US within the next few years.

Long term survival from pancreatic cancer is rare, and no cure for pancreatic cancer has been discovered. By identifying and screening patients at increased risk for harboring or developing pancreatic cancer (pancreatic cysts, hereditary pancreatic cancer, chronic pancreatitis, certain genomic-based disorders), there is hope of early detection and prevention of pancreatic cancer for a substantial number of individuals.

Assessment of clinical, radiographic, and cytopathologic features of pancreatic cystic lesions is the standard of care for identification of pancreatic cystic neoplasms, proper cancer risk stratification, and appropriate management of patients with pancreatic cystic lesions. Symptomatic patients have a greater incidence of pancreatic cancer development, especially with symptoms/signs of pancreatic exocrine or endocrine failure. In terms of radiographic parameters, arguably the most important indicator of malignancy is the presence of main pancreatic duct (MPD) dilation. The extent of MPD dilation is directly proportional to pancreatic cancer risk. Although the degree of MPD dilation predicts pancreatic cancer risk, branch duct or cyst size is no longer considered a reliable indicator of malignant potential. Another very specific radiographic indicator of malignancy is the presence of mural nodules within the cystic lesion. While quite specific, mural nodules are not, however, very sensitive, because they are present in only 30 % of pancreatic cystic neoplasms harboring invasive cancer. Mural nodules suspected on static imaging (MRI, CT) should be confirmed by dynamic imaging (EUS) to exclude mobility; if mobile, these "nodules" are likely to be debris/mucin and thus, not associated with the same cancer risk. High grade atypia on cytopathology is highly specific for the presence of malignant cells in the pancreatic cyst either as *carcinoma*-in-situ or invasive carcinoma; however, high

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grade atypia is not very sensitive, because only 50 % of invasive mucinous cystic neoplasms have high grade atypia recognizable in the samples of the cyst fluid. Accordingly, we maintain that formal resection should be performed in fit patients with new or worsening symptoms, mural nodules, progressive MPD dilation, and high grade dysplasia on cytopathology. These parameters, however, by themselves are not sufficient to guide our management of these patients (Cauley et al. 2012; Miller et al. 2011). Patients without these parameters have developed invasive cancer in pancreatic cystic lesions. The only clues in these patients have often been subtle changes in serum tumor markers, such as alkaline phosphatase, amylase, lipase, CA19-9, and hemoglobin a1c. These serum markers alone are unlikely to insure early detection, but serial determination of these serum markers is reasonable and deserves further study. Clearly, we need better indicators to guide our management of these patients.

Most recently, the collective knowledge of patients with pancreatic cystic lesions is moving forward at a tremendous pace. Biochemical and more recently molecular marker discovery in pancreatic cystic fluid appears to be most promising. Such novel and exciting analyses may diagnose and/or assess malignant potential.

Two useful markers in pancreatic cyst fluid currently are CEA and Kras. CEA level >192 ng/ml is consistent with a mucinous cystic neoplasm (IPMN or MCN). CEA is a widely available diagnostic biochemical test. CEA level in the cyst fluid does not predict the presence of malignancy but does predict cystic lesions with malignant potential. Kras mutations when detected also indicate the presence of a mucinous pancreatic cyst. The combination of CEA and Kras in the cystic fluid is nearly 100 % predictive of a mucinous cystic neoplasm of the pancreas and discriminates between cystic neoplasms and pseudocysts or other benign cysts.

More recently, a molecular profile of DNA mutations (Pathfinder TG™, RedPath, Inc.) present at multiple pancreatic cancer relevant genetic loci (e.g., KRas, p53, DPC4, P16, PTEN, 17q, etc.) was developed." This profile is commercially available now to provide serial quantification of the malignant potential of pancreatic cystic lesions. When the mutation panel is tested on known pancreatic cancers, >3 of these mutations are typically detected.

A newly discovered molecular marker in pancreatic cyst fluid is GNAS (Wu et al. 2011a), which is the oncogene encoding guanine nucleotide regulatory protein S alpha (GSα). GNAS mutations (i.e., codon 201: R201H or R201C) are diagnostic of IPMN but are present in only 66 % of IPMNs. When combined with analysis of Kras mutations, either GNAS and/or Kras mutations are present in 95 % of IPMNs (Wu et al. 2011a). Another newly discovered molecular marker is RNF43 which is expressed in the cyst epithelium in 75 % of IPMNs and 38 % of MCNs examined (Wu et al. 2011b). RNF43 is a tumor suppressor gene which encodes for a protein with intrinsic E3 ubiquitin ligase activity on chromosome 17q. Interestingly, 17q is the location of one of the genetic loci examined currently with the Pathfinder TG™. The development of miRNA profiling of pancreatic cyst fluid holds promise as a predictor of malignant potential in pancreatic cystic lesions but awaits further validation (Ryu et al. 2011). Finally, a recently discovered diagnostic marker $VEGF_{B9}$™ (B9, Inc.) an isoform of VEGF A, when present in pancreatic cyst fluid at a threshold level, approaches 100% accuracy in diagnosing the uniformly benign serous cystic neoplasms thereby altering the necessity of surveillance and possibly pancreatectomy in patients with cystic lesions of uncertain diagnosis. In summary, biochemical (CEA) and molecular (Kras, Pathfinder TG™) profiling, including the newly discovered markers GNAS, RNF43, miRNA and $VEGF_{B9}$ offer the potential to transform how we manage patients with pancreatic cystic lesions.

While we are looking for a cure for pancreatic cancer, it is equally critical to identify and screen patients at increased risk of pancreatic malignancy (family history, pancreatic cysts) to promote both early detection and prevention of advanced pancreatic cancer.

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