ADVANCES IN ENDOSCOPY

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Novel Endoscopic Techniques for the Diagnosis of Pancreatic Cysts

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G&H How are pancreatic cysts classified?

SK Pancreatic cysts are classified into mucinous and nonmucinous categories. The mucinous classification tends to imply precancerous lesions, and includes intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms. IPMNs are the most common type of precancerous cyst, accounting for nearly 80% of all mucinous cysts. They are especially common among patients 60 years of age and older.

Nonmucinous cysts are typically considered to be benign, although that is slightly misleading. Among the cysts in this classification are pseudocysts, which are a result of prior acute pancreatitis and never become malignant. Although serous cystadenomas are neoplastic, they hardly ever become malignant and are therefore considered benign neoplastic cysts. Both pseudocysts and serous cystadenomas are the most common types of nonmucinous pancreatic cysts. Uncommon types of nonmucinous cysts are cystic neuroendocrine tumors and solid pseudopapillary neoplasms, both of which have the potential to turn malignant. While solid pseudopapillary neoplasms are always surgically resected, cystic neuroendocrine tumors are surveyed and resected depending on patient demographics, tumor functioning status, and their size, with most ending up being resected.

G&H How have pancreatic cysts traditionally been diagnosed?

SK Pancreatic cysts tended to be diagnosed incidentally, but rather rarely, on imaging studies. Advanced cysts were diagnosed when precancerous cells progressed to cancer or caused symptoms such as jaundice (via compression of the bile duct) or diabetes, weight loss, abdominal pain, or acute pancreatitis (via compression of the pancreatic duct). However, within the last 10 to 15 years, imaging technology has improved and cross-sectional imaging with computed tomography (CT) scans or magnetic resonance imaging (MRI) is more frequently performed. This has led to a marked increase in the incidental diagnosis of pancreatic cysts, and data have shown that nearly 2% to 5% of abdominal CT scans and nearly 35% to 40% of abdominal MRIs identify cysts in the pancreas.

G&H How are pancreatic cysts managed?

SK Major societies, such as the American Gastroenterological Association and the American College of Gastroenterology, have published guidelines within the last 5 years on how to manage cysts. The most commonly followed guidelines are the International Consensus Guidelines, which were last revised in 2017. In general, the size of the pancreatic cyst determines how it is managed. Cysts smaller than 1 cm can be followed with imaging studies. If cysts are between 1 and 2 cm, gastroenterologists should consider adding endoscopic ultrasound (EUS) for evaluation. Anything larger than 2 cm should certainly undergo evaluation with EUS. Traditionally, and in most facilities

across the United States, endoscopists will also perform fluid aspiration for cysts larger than 2 cm. The fluid is sent to a cytologist for cytologic evaluation and tumor marker testing, specifically for carcinoembryonic antigen (CEA). The main benefit associated with cyst fluid analysis is the relatively inexpensive cost due to using basic EUS and fine-needle aspiration. However, the overall accuracy for differentiating mucinous from nonmucinous cysts is 65% to 70%, meaning nearly 30% of cysts are not accurately classified. Furthermore, the basic standard-of-care analysis typically does not reveal if an IPMN has presence of advanced neoplasia (ie, high-grade dysplasia or adenocarcinoma).

G&H What endoscopic approaches are currently available to diagnose pancreatic cysts?

SK Beyond the traditional methods of cross-sectional and EUS imaging–guided cyst morphology, EUS-guided fine-needle aspiration, and analysis of cyst fluid CEA and cytology, there are multiple novel endoscopic approaches. The 3 most common techniques that are being studied are cyst fluid molecular analysis, which utilizes next-generation sequencing (NGS), EUS-guided confocal laser endomicroscopy, and EUS-guided through-the-needle forceps biopsy. While cyst fluid molecular analysis can be obtained from standard EUS-guided fine-needle aspiration of the cyst using a 22-gauge needle, both confocal laser endomicroscopy and through-the-needle forceps biopsy require a larger 19-gauge needle. During EUS-guided confocal laser endomicroscopy, a mini endomicroscopy probe (<1 mm in diameter) is preloaded through the 19-gauge needle. Once the needle is in the cyst and approaches the opposite wall, the mini-probe is advanced beyond the needle tip for visualizing the inner lining, or epithelium, of the cyst. Specific cyst types produce unique diagnostic black-and-white microscopy imaging. Training is needed to perform and interpret endomicroscopy imaging. A similar, large-caliber 19-gauge needle is used for EUS-guided through-the-needle forceps biopsy. Once the needle is in the cyst, tiny forceps are introduced through the needle and are used to take a small biopsy from the wall of the cyst. The biopsy is then sent to a pathologist for examination.

G&H How do these newer approaches compare to conventional methods for detecting and diagnosing pancreatic cysts?

SK There is an overall improved diagnostic accuracy with the novel methods compared to the current standard of care. The 3 modalities discussed previously each have an approximate minimum accuracy rate of 90% for classifying a cyst as mucinous or nonmucinous. The novel modalities can also diagnose the specific cyst type. Moreover, several of these modalities, including cyst fluid molecular analysis and EUS-guided confocal laser endomicroscopy, can potentially risk-stratify IPMNs into those with or without advanced neoplasia. Most of the research in the risk stratification of cysts is with molecular analysis of cyst fluid.

G&H How do the novel approaches compare to the standard of care in terms of safety, feasibility, and accuracy?

SK The standard EUS-guided cyst fluid aspiration is fairly safe and risk-free when using a smaller-caliber needle (eg, 22-gauge). Cyst fluid molecular analysis, which also uses a 22-gauge needle, is similarly safe. The most common adverse event is mild acute pancreatitis, occurring in less than 1% of patients. Initially, the risk of cyst infection was thought to be high, but recent research has shown that this risk is negligible. Hence, endosonographers differ in using prophylactic antibiotics either during or following the EUS procedure. EUS-guided confocal endomicroscopy and EUS-guided through-the-needle biopsy, which both use the larger-caliber 19-gauge needle, are associated with an increased risk of adverse events, particularly acute pancreatitis. Published studies have reported a 2% to 5% risk of acute pancreatitis with EUS-guided confocal laser endomicroscopy, with the first 24 hours following the procedure carrying the highest risk. Three large meta-analyses have shown that the risk of adverse events with EUS-guided through-the-needle biopsy is approximately 6% to 10%. The most common adverse event is intracystic bleeding (50%-75%), followed by acute pancreatitis (approximately 25%). My colleagues and I recently published our single-center experience in *Clinical Gastroenterology and Hepatology* in which there were 5 cases of acute pancreatitis among 144 patients, and 4 of the 5 were in the first 25 cases. Thus, there is a learning curve; the 19-gauge needle is much stiffer and it takes some technical skill to learn how to use it. As endoscopists become more familiar with using a 19-gauge needle, I think the risk of adverse events will decrease.

As for feasibility, acquiring fluid with a 22-gauge needle for either cyst fluid CEA or cyst fluid molecular analysis is generally 100% possible, although intervening blood vessels may cause challenges. Using the 19-gauge needle for confocal endomicroscopy and through-the-needle biopsy can pose some difficulty, especially in cysts that are located in the deep uncinate process. Our single-center experience demonstrated that confocal

endomicroscopy is technically feasible in 97% of patients; 4 out of 150 patients were unable to undergo the procedure because of the deep uncinate location of the cysts. According to recent meta-analyses, through-the-needle biopsy has a technical feasibility rate of 95% to 98%.

The accuracy of molecular analysis for identifying mucinous vs nonmucinous cysts has been reported in multiple studies. A single-center prospective study from the University of Pittsburgh of 102 patients who had surgical resection reported a sensitivity of 89% and specificity of 100%. My colleagues and I studied 31 patients and demonstrated an accuracy of 90%, sensitivity of 88%, and specificity of 100%. Confocal endomicroscopy has been shown to have an accuracy of approximately 97% for differentiating mucinous from nonmucinous cysts, with a sensitivity of 98% and specificity of 94%. The accuracy of through-the-needle biopsy depends on specific diagnosis and diagnostic yield, the latter of which is used because studies tend to have very few patients with definitive surgical histopathology to compare as a gold standard. For definitive diagnosis, the diagnostic yield ranges from 70% to 78%, with a specimen adequacy rate (meaning that the pathologist had enough specimen to evaluate and diagnose) of 82% to 85%.

G&H What work is currently being done in the setting of IPMNs?

SK As stated previously, IPMNs are the most common precancerous cysts and are highly prevalent in individuals 60 years of age and older. IPMNs tend to be very problematic and can cause undue anxiety to the treating physician if he or she typically does not manage pancreatic issues. Traditional and novel diagnostics play an important role. Using traditional standard-of-care modalities (MRI and EUS), gastroenterologists can follow the International Consensus Guidelines to risk-stratify cysts. The addition of novel diagnostics can improve risk stratification, and much work is being done in this area. When evaluating the use of molecular analysis or NGS, researchers from the University of Pittsburgh found that the combination of *KRAS* and *GNAS* mutations, with additional mutations in *TP53*, *PIK3CA*, and *PTEN*, had an 88% sensitivity and 97% specificity for identifying IPMNs with advanced neoplasia. Furthermore, mutations in *TP53*, *PIK3CA*, and *PTEN* showed a 79% sensitivity and 96% specificity for all mucinous pancreatic cysts with advanced neoplasia, including IPMNs and mucinous cystic neoplasms, demonstrating the potential for the role of molecular analysis in risk-stratifying cysts. Importantly, single-center studies need to be reproduced in multicenter studies, a task that the research team at the University of Pittsburgh is currently undertaking.

My colleagues and I published a study in *Gastrointestinal Endoscopy* showing that the papillae that are seen during confocal endomicroscopy can be used for risk stratification. If the papillae are very thin and translucent, they have low-grade dysplasia, but as the papillae grow bigger, they get thicker and darker (stratification of cells and nuclei), which is suggestive of higher grades of dysplasia. Our study of 26 patients with surgically resected IPMNs demonstrated a sensitivity of 88% and specificity of 100% for diagnosing advanced neoplasia. When we used the traditional International Consensus Guidelines, the sensitivity was 56% and specificity was 100%. Using the American Gastroenterological Association guidelines, the sensitivity was 56% and specificity was 80%. Thus, confocal endomicroscopy had higher accuracy than the standard of care.

Currently, there is a lack of studies using through-the-needle biopsy to risk-stratify IPMNs.

G&H What criteria should be used to determine which approach is the most appropriate?

SK The answer depends on the center and what procedures it tends to follow. Each center has its own protocol based on what it can do—whether endoscopists are limited by just using standard of care (fluid aspiration, sending for CEA or cytology) or if they can send cyst fluid for molecular analysis, or if there are experts who can perform through-the-needle biopsy or confocal endomicroscopy. For through-the-needle biopsy, the biopsy forceps themselves are not reimbursed, and although they are relatively inexpensive, they are still an additional cost. The forceps are single-use and require some procedural skill. In general, most advanced endoscopists can easily obtain biopsies of the cyst wall. There are certain particular details as far as trying to pinch the epithelium, making it tent, and pulling it for tissue adequacy that can make it more challenging. Endomicroscopy requires a processor, which can be obtained on a lease basis without upfront costs or it can be purchased. The probes for performing endomicroscopy also need to be purchased, and a single probe can be used in 10 patients. The billing code that is used for optical endomicroscopy factors in the cost of the probe, so the facility is compensated for that. Besides having the equipment, training is needed for image interpretation, as gastroenterologists are not trained in this area during their advanced endoscopy fellowship. Each of the cyst types has a unique image pattern, and courses or online conferences are needed to make sense of the image feed from the inside of the cyst.

In general, cysts smaller than 1 cm require no intervention and need to be observed. Cysts between 1 and 2 cm can be surveyed based on imaging morphology. Some

facilities that can perform molecular analysis may aspirate the cyst with a fine needle and send the fluid for CEA testing and NGS, the latter of which is fairly accurate for IPMNs but not so much for mucinous cystic neoplasms and serous cystadenomas. When the cysts are between 2 and 3 cm, there is a gradually increased need for accurate diagnosis and risk stratification. Therefore, advanced modalities such as endomicroscopy and through-the-needle biopsy can be useful. Once the cyst is 3 cm or larger, an accurate diagnosis and risk stratification is needed to either cease follow-up (if the cyst is a benign pseudocyst or serous cystadenoma), recommend surgical resection (if the cyst is mucinous and demonstrates worrisome and/or high-risk features), or continue intense surveillance (imaging or EUS every 3-6 months). For example, if the cyst is an IPMN in the head of the pancreas and novel diagnostics reveal presence of advanced neoplasia, a major surgical procedure such as the Whipple procedure should be considered.

G&H What are the priorities of research in this field?

SK There is a critical need to provide accurate diagnosis of pancreatic cysts and avoid unwarranted pancreatic surgery or wrongly diagnosing a cyst as benign. In addition, accurate risk stratification of IPMNs is necessary, as 2 large surgical series have shown that nearly 40% of resected IPMNs tend to have low-grade dysplasia. Pancreatic surgery has an overall mortality of a little less than 1% and a morbidity of nearly 20% to 40%. Resection of the head of the pancreas is associated with a higher risk of exocrine insufficiency, causing malabsorption and/or diarrhea. While the risk of new onset of diabetes after pancreatectomy is around 18% to 20%, the risk is higher following distal pancreatectomies. Thus, accurate risk stratification of the more common cysts such as IPMNs is critical as we move into the future. New data are emerging on the EUS-guided ablation of cysts, mostly from Asia and from some centers in the United States. Several studies are underway, and, hopefully, there will be appropriate ablative chemotherapy drugs in the next 5 to 10 years that can be injected into the cysts during EUS. These ablative therapies can potentially avoid pancreatic surgeries in patients with high surgical risks.

Disclosures

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Suggested Reading

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