Role of endoscopic ultrasound for pancreatic cystic lesions: Past, present, and future!

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The differential diagnosis of pancreatic cystic lesions is diverse and includes a variety of causes including pseudocysts, serous cyst adenomas, mucinous cystic neoplasms, intraductal papillary mucinous neoplasms, neuroendocrine tumors, lymphoepithelial cysts, and cystic degeneration of solid tumors. In this special issue of the Endoscopic Ultrasound (EUS) Journal, it has been my privilege to invite experts and pioneers from around the world to discuss and present in detail the various applications of EUS for the evaluation of pancreatic cystic lesions.

Prior to the development of EUS, only those pseudocysts could be drained endoscopically that had a subepithelial compression of the stomach or duodenum; endoscopic drainage always required fluoroscopy without the ability to see intervening vessels. EUS has revolutionized the treatment of pancreatic pseudocysts. Saftoiu, Vilmann, and Vilmann from Romania and Denmark[1] present the data on the history of pancreatic pseudocyst drainage by EUS, success rates, and safety and comparative trials with surgery/non-EUS guided endoscopic techniques. The recent interest in development by industry (in collaboration with physician pioneers) of devices tailor-made for EUS-guided therapy has further enhanced EUS drainage of pancreatic pseudocysts, and even other complicated pancreatic fluid collections such as walled-off pancreatic necrosis.

EUS provides us with an enhanced ability to study the cyst wall and the internal echo characteristics of a cystic pancreatic tumor. Septations, solid areas, mural nodules, and papillary projections as well as connections to the main or side branches of the pancreatic duct can be seen. Hijioka *et al.*[2] from Japan and India discuss the various morphological characteristic features of different pancreatic cystic neoplasms. The high resolution imaging by EUS not only allows us to study the cystic lesion in question but also to study the pancreatic ductal system. EUS can be used for follow-up of cystic lesions for change in ultrasonographic (echo) features that may predict progression to malignancy. EUS diagnostic capability is further improved by contrast-enhanced EUS that can, for example, differentiate a solidified mucin nodule from a true solid mural module based on enhancement pattern.

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While EUS of pancreatic cysts provides high resolution images, there is an overlap of morphological features between various benign, premalignant, and malignant cystic neoplasms of the pancreas. EUS-guided fine-needle aspiration (FNA) provides an opportunity to further enhance the diagnosis for medical decision-making. Is EUS-guided FNA of pancreatic cystic tumors safe? Yoon and Brugge[3] from the USA and Korea provide us with a review of the safety of EUS-FNA of pancreatic cysts. The overall risk of complications is low and around 2%. Infectious complications can be mitigated by the use of prophylactic antibiotics. More importantly, the authors discuss the even more controversial issue of peritoneal seeding that has been raised by colleagues in Japan based on a few cases reports. The PIPE study by the same group in the USA (led by Professor Brugge) looking the at seeding issue is discussed in this review that is dedicated solely to the safety of EUS-FNA.

Once EUS-FNA of a suspected cystic pancreatic neoplasm is performed, a number of things can be studied and analyzed in the cyst fluid. Sending the fluid for cytology could provide an accurate diagnosis but in comparison to solid pancreatic neoplasms, cystic tumors have limited shedding of cells and thus, the sensitivity of cytology leaves much to be desired. Therefore, we need to look at other techniques such as viscosity and carcinoembryonic antigen (CEA) levels in the pancreatic cyst fluid. CEA to date is the most widely done and well-studied marker in pancreatic cyst fluid. Alkaade, Chahla, and Levy[4] from the USA have nicely reviewed the accuracy, limitations, and issues with the use of cytology, viscosity, and CEA in the pancreatic cyst fluid.

While CEA in pancreatic cyst fluid is useful, it also has limitations. We clearly need more markers that can reliably differentiate a benign cystic lesion from a premalignant/malignant lesion, and ideally a premalignant from a malignant cystic lesion. This is a hot topic of research at this time. Dr. Al-Haddad[5] from the United Arab Emirates has provided an elegant review of the data and emerging applications of various molecular markers in pancreatic cyst fluid including KRAS and tumor suppressor gene mutations, GNAS oncogene, microRNAs, various interleukins, and others.

Confocal laser endomicroscopy (CLE) has enabled real-time imaging during endoscopy at the subcellular level providing an *in vivo* optical biopsy. Probes can be passed through biopsy channels of endoscopes for imaging of Barrett's, colitis, polyps, and neoplasms. This technique is further miniaturized with needle CLE with a 0.632-mm needle confocal laser endomicroscopy (nCLE) probe that can be passed through a 19G EUS needle into solid and cystic masses under EUS guidance. Professor Giovannini[6] from France has reviewed the application of nCLE for pancreatic cystic lesions in terms of accuracy and safety. The images obtained for serous cyst adenoma with the superficial vascular network and intraductal papillary mucinous neoplasm (IPMN) with papillary projections are very specific. Sensitivity is however, not that high and needs to improve. The criteria for other cystic pancreatic tumors such as neuroendocrine tumors are being developed. The developments are quite exciting, novel, and add to various developing techniques for assessment of cystic pancreatic neoplasms. Perhaps in the future, malignant and benign IPMNs can be differentiated based on these kinds of optical biopsy techniques.

It is not possible or necessary to perform surgery on every pancreatic cyst that is detected by EUS. It would be fantastic if a safe minimally invasive nonsurgical method could be available for treating some pancreatic cystic neoplasms. This could include ablating the epithelium for cysts that have dysplasia or even early cancer. This would be akin to removing adenomatous colon polyps or early colon cancer endoscopically that we do routinely at present. We ablate Barrett's esophagus with radiofrequency ablation now when high grade (and even persistent low grade) dysplasia is present to prevent progression to cancer and we treat early esophageal cancer with endoscopic mucosal resection. Cho, Choi, and Seo from the Republic of Korea[7] reviewed the data on attempts to endoscopically ablate pancreatic cysts with alcohol and chemotherapeutic agents under EUS guidance. The short-term data on efficacy of these techniques is promising but we do need more long-term data before routine widespread application. Even EUS-guided radiofrequency ablation of the cysts may be possible based on some early human reports. These ablative techniques may be applied in patients who otherwise need surgery due to worrisome features, symptoms, or proven malignancy but are not surgical candidates. Other patients with cysts that are considered to have extremely high risk for progression of malignancy could potentially be ablated with chemical or thermal means to prevent progression to cancer. For the present, endoscopic ablation of pancreatic cystic tumors in most

instances should be considered experimental and not the standard of routine care.

To summarize, EUS has emerged as an extremely valuable tool for the imaging, diagnosis, and therapy of pancreatic cystic lesions including neoplasms and pseudocysts. Numerous advances have been made, thanks to the work of many pioneering endosonographers from around the world who have written the papers in this special edition or whose work has been cross-referenced in this issue. It has been my privilege and honor to edit this dedicated issue of the EUS journal on the role of endosonography in pancreatic cystic lesions. In the future, we hope that advances in research will even further enhance the role of EUS for pancreatic cystic neoplasms. An ideal situation would be to have a personalized or individualized medicine type approach for pancreatic cystic neoplasms. If the combination of cytology, nCLE, and various emerging molecular markers in the cyst fluid can predict with near certainty the patient who has high grade dysplasia or early cancer, or who is likely to progress to malignancy rapidly, then we can not only selectively target these patients for more intensive surveillance, endoscopic ablation, or surgery but also back off from closely watching, imaging, or performing invasive procedures on the rest of the asymptomatic pancreatic cyst population at large.

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