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Authors

Lee, Linda S
Andersen, Dana K
Ashida, Reiko
et al.

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EUS and related technologies for the diagnosis and treatment of pancreatic disease: research gaps and opportunities—Summary of a National Institute of Diabetes and Digestive and Kidney Diseases workshop

Linda S. Lee, MD[1], **Dana K. Andersen, MD**[2], **Reiko Ashida, MD, PhD**[3], **William R. Brugge, MD**[4], **Mimi I. Canto, MD**[5], **Kenneth J. Chang, MD**[6], **Suresh T. Chari, MD**[7], **John DeWitt, MD**[8], **Joo Ha Hwang, MD, PhD**[9], **Mouen A. Khashab, MD**[5], **Kang Kim, PhD**[10], **Michael J. Levy, MD**[7], **Kevin McGrath, MD**[11], **Walter G. Park, MD**[12], **Aatur Singhi, MD, PhD**[13], **Tyler Stevens, MD**[14], **Christopher C. Thompson, MD, MHES**[1], **Mark D. Topazian, MD**[7], **Michael B. Wallace, MD, MPH**[15], **Sachin Wani, MD**[16], **Irving Waxman, MD**[17], **Dhiraj Yadav, MD, MPH**[12], **Vikesh K. Singh, MD, MS**[5]

[(1)]Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts [(2)]Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland [(3)]Departments of Cancer Survey and Gastrointestinal Oncology, Osaka Prefectural Hospital Organization, Osaka International Cancer Institute, Osaka, Japan [(4)]Department of Gastroenterology, Massachusetts General Hospital, Boston, Massachusetts [(5)]Division of Gastroenterology, Johns Hopkins University School of Medicine, Baltimore, Maryland [(6)]Comprehensive Digestive Disease Center, Department of Gastroenterology and Hepatology, University of California at Irvine Health, Orange, California [(7)]Department of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota [(8)]Division of Gastroenterology, Indiana University Health Medical Center, Indianapolis, Indiana [(9)]Department of Medicine, University of Washington, Seattle, Washington [(10)]Department of Medicine, University of Pittsburgh [(11)]Division of Gastroenterology, Hepatology, and Nutrition, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania [(12)]Department of Medicine, Stanford University School of Medicine, Stanford, California [(13)]Department of Pathology, University of Pittsburgh Medical Center, Sewickley, Pennsylvania [(14)]Department of Gastroenterology, Cleveland Clinic, Cleveland, Ohio [(15)]Department of Gastroenterology and Hepatology, Mayo Clinic Florida, Jacksonville, Florida [(16)]Division of Gastroenterology and Hepatology, University of Colorado Anschutz Medical Campus, Aurora, Colorado [(17)]Department of Medicine, The University of Chicago Comprehensive Cancer Center, University of Chicago School of Medicine, Chicago, Illinois

Abstract

A workshop was sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases to address the research gaps and opportunities in pancreatic EUS. The event occurred on July 26, 2017 in 4 sessions: (1) benign pancreatic diseases, (2) high-risk pancreatic diseases, (3)

Reprint requests: Linda S. Lee, MD, Brigham and Women's Hospital, 75 Francis St. Boston, MA 02115.

diagnostic and therapeutics, and (4) new technologies. The current state of knowledge was reviewed, with identification of numerous gaps in knowledge and research needs. Common themes included the need for large multicenter consortia of various pancreatic diseases to facilitate meaningful research of these entities; to standardize EUS features of different pancreatic disorders, the technique of sampling pancreatic lesions, and the performance of various therapeutic EUS procedures; and to identify high-risk disease early at the cellular level before macroscopic disease develops. The need for specialized tools and accessories to enable the safe and effective performance of therapeutic EUS procedures also was discussed.

EUS became commercially available in the 1980s with the seminal publications by DiMagno et al[1] and Hisanaga et al[2,3] demonstrating the feasibility and safety of mounting an US transducer on the tip of a rigid endoscope and using this to examine the GI wall and extraluminal space. Since then, EUS with the addition of FNA has established itself as the premier diagnostic tool for staging many GI luminal cancers, evaluating intramural lesions, and assessing the immediate extraluminal space. It has assumed particular importance in the diagnosis of pancreatic cancers as well as other pancreatic diseases and more recently has evolved into a key vehicle for a variety of therapeutic procedures. The National Institute of Diabetes and Digestive and Kidney Diseases workshop, “Endoscopic ultrasound and related technologies for the diagnosis and treatment of pancreatic disease: research gaps and opportunities,” sought to review the latest knowledge and set priorities for future investigation.

EUS remains the diagnostic test of choice for diagnosing pancreatic masses. Although some advocate for surgical resection without biopsy, sampling these masses to determine the exact diagnosis remains important because a significant minority of these patients do not have pancreatic adenocarcinoma and those who do are increasingly requiring precision therapy. Nearly 15% of pancreatic masses are metastatic lesions, with another 1% to 2% being lymphomas and 5% to 11% autoimmune pancreatitis. Neoadjuvant therapy may improve outcomes, with 46% of borderline resectable tumors converted to resectable lesions after therapy.[4] Concerns over the potential spread of malignant cells by performing EUS-guided FNA (EUS-FNA) of pancreatic masses were assuaged by a study demonstrating that EUS-FNA was not associated with decreased survival.[5] The ideal technique to ensure the highest diagnostic yield remains unclear and will be discussed in greater detail below. Recent innovations in core needles may enable acquisition of increased amounts of tissue required for molecular assays compared with conventional FNA needles.

Performance of EUS in pancreatic cysts remains controversial, with several guidelines offering, at times, discrepant recommendations for indications of EUS.[6–8] This stems from the inability of currently available cyst fluid analyses to diagnose and accurately predict the malignant potential of these cysts. Therefore, translational research has flourished, with investigations involving proteomics, metabolomics, and DNA and RNA analyses all demonstrating a variety of promising markers including DNA methylation markers to discriminate cysts with malignancy or high-grade dysplasia from those with low-grade or no dysplasia.[9] Large prospective validation studies are required to establish which markers or combination of markers would be most efficacious.

Another problematic area involves the diagnosis of chronic pancreatitis, with the American Pancreatic Association practice guidelines concluding that EUS features of chronic pancreatitis may represent not only chronic pancreatitis but also pancreatopathy, an asymptomatic presence of fibrosis without inflammation caused by a variety of factors including aging and exposure to alcohol or smoking.[10] Furthermore, interobserver agreement among experienced endosonographers for various chronic pancreatitis features remains inadequate despite the more recent Rosemont criteria.[11,12] Autoimmune pancreatitis (AIP) is another condition in which EUS may be helpful but remains difficult to diagnose and differentiate from pancreatic adenocarcinoma (PDAC).

EUS-guided therapeutics began with celiac plexus neurolysis, which has proven effective and durable in treating pancreatic cancer pain. Initial reports of the surgical technique in which patients were randomized in a double-blind study to neurolysis with 50% alcohol compared with saline solution interestingly demonstrated not only improved pain control through 6-month follow-up but also increased survival in these patients, which remains poorly understood.[13] A randomized trial comparing conventional pain management to EUS-guided celiac plexus neurolysis also reported improved pain control, although there was no difference in quality of life.[14]

Another well-established therapeutic intervention with EUS is drainage of pseudocysts and walled-off pancreatic necrosis. Standard of care in initial management of these conditions has dramatically evolved from surgical drainage and debridement to endoscopic and percutaneous approaches. However, controversy still exists about when, in whom, and how to perform endoscopic necrosectomy. Recent interest has centered around the use of lumen apposing metal stents (LAMSs) to facilitate these procedures, with some studies suggesting increased rates of bleeding associated with LAMS placement.[15] Multiple retrospective studies have published discrepant findings with respect to success of procedures and need for repeat procedures when LAMSs are compared with plastic stents.[16–18] Large prospective randomized trials are needed to understand the best setting for each type of stent.

The National Institute of Diabetes and Digestive and Kidney Diseases workshop occurred at an important time when EUS of the pancreas has established itself as the optimal diagnostic and therapeutic technique for a variety of pancreatic diseases but requires further development in several critical areas including pancreatic cystic lesions, chronic pancreatitis, fatty pancreas, early detection of high-risk pancreatic lesions, and various therapeutics. The lectures and sessions provided expert analyses of the issues facing EUS of the pancreas in the 21st century as well as a framework for next steps needed to advance the field forward.

EUS PERFORMANCE AND INTERPRETATION IN BENIGN PANCREATIC DISEASES

Overview of the problem

EUS is a technically challenging procedure that requires advanced training beyond those required for performing upper and lower endoscopy. These aspects contribute to operator variability that impacts competency and diagnostic interpretation of several benign

pancreatic disorders including chronic pancreatitis, autoimmune pancreatitis, and fatty pancreas.

Assessing competency in pancreatic EUS

EUS is taught predominantly by apprenticeship, with competence primarily measured by procedure volume. Although the threshold volume varies among societies, the American Society for Gastrointestinal Endoscopy has defined this as 225 cases before competency can be assessed.[19] This target is based on expert opinion and does not account for the different rates at which trainees learn. Data from a multicenter study that used a validated skills assessment tool—The EUS and ERCP Skills Assessment Tool, with cumulative-sum analysis, demonstrated substantial variability among trainees in achieving competence in EUS, and suggested that competence is not assured after completing 225 cases with 76% to 82% achieving cognitive and technical competence.[20]

These results highlight the limitation of volume-based competency metrics and indicate that EUS training needs to evolve toward a curriculum that focuses on competence-based medical education—a reform promoted by the Accreditation Council for Graduate Medical Education-Next Accreditation System. These reforms would include establishing minimum standards for advanced endoscopy training programs that incorporate trainee assessment through competency-based milestones of both technical and cognitive skills. It would also include education on systematically measuring and monitoring EUS performance against defined metrics of a high-quality EUS examination.[21] Limited exposure to therapeutic EUS techniques during training necessitates the development of specific training strategies to address this issue as well.

EUS in differentiating normal pancreas, minimal change chronic pancreatitis, and other pancreatopathies

In clinical practice, the diagnosis of chronic pancreatitis is typically made when obvious parenchymal and/or ductal changes in the pancreas are apparent on cross-sectional studies, that is, CT and/or magnetic resonance imaging (MRI)/MRCP). These changes, however, may occur at variable times (sometimes years) after the onset of clinical symptoms. *Minimal change chronic pancreatitis* is a term used to describe patients who have symptoms suggestive of chronic pancreatitis, most commonly chronic abdominal pain, but normal or equivocal cross-sectional imaging test results. In these patients, diagnosing chronic pancreatitis remains challenging and may be aided by identifying parenchymal and/or ductal changes on EUS.

The criteria used to diagnose chronic pancreatitis on EUS includes a non-weighted and weighted score that incorporates stricter definitions for minor and major features, which appear to reflect pancreatic fibrosis.[22] However, establishing a diagnosis of chronic pancreatitis solely by using EUS has limitations. EUS may play a role as part of a more comprehensive diagnostic model incorporating various risk factors for chronic pancreatitis.[23] There remains high interobserver variability for individual findings and overall scoring among experienced endosonographers.[12] Several conditions, including increasing age, smoking, alcohol consumption, and diabetes may cause parenchymal and/or ductal changes

without symptoms (defined by the term *pancreatopathy*),[23,24] making it difficult to determine if changes observed on EUS result from chronic pancreatitis or merely from these confounding factors. Studies have compared EUS features with MRCP (with or without secretin), secretin-stimulated pancreatic function testing, and histology.[25] Although some comparisons are promising, the lack of a criterion standard and the role of confounding factors have not been appropriately addressed.

EUS in differentiating mass-forming autoimmune pancreatitis from pancreatic cancer

Autoimmune pancreatitis (AIP) is a relatively rare form of chronic pancreatitis that afflicts not only the pancreas but also other organs including the bile duct. Both AIP and chronic pancreatitis may present with focal mass-forming disease that can mimic PDAC, and accurate distinction of these 3 disease processes is important for providing disease-appropriate care and for enhancing patient outcomes.[26] Patients with unrecognized AIP or chronic pancreatitis continue to undergo pancreatic resection for presumed malignancy. In addition, delayed or failed diagnosis of AIP risks allowing disease progression to chronic pancreatitis changes. Although many studies have evaluated the accuracy of EUS for diagnosing PDAC and for assessing chronic pancreatitis ductal and parenchymal features, there is a paucity of data evaluating EUS features of AIP as well as the ability of EUS to distinguish among these disease processes.

Well-designed studies are needed to evaluate the capability of EUS for diagnosing and distinguishing AIP, chronic pancreatitis, and PDAC based on conventional and potentially new EUS imaging criteria and to evaluate EUS-associated technologies such as elastography, contrast-enhanced imaging, and computer-aided techniques.[27] Understanding the potential utility of EUS to distinguish type 1 and 2 AIP and to predict therapeutic response is also warranted. Studies that clarify the relative value of EUS-guided cytologic versus histologic diagnosis by using an appropriate pathology criterion standard are needed.

EUS and fatty pancreas

Existence of fat in the pancreas has been known since the 1930s, although the true prevalence remains unknown. *Fatty pancreas* is a radiologic term that describes the presence of excess intrapancreatic fat (IPF). Different terms have been used to describe fatty pancreas including pancreatic steatosis, non-alcoholic fatty pancreas disease, pancreatic lipomatosis, lipoatrophy of the pancreas, pancreatic fatty infiltration, and pancreatic fatty replacement. Although fatty pancreas is common in certain genetic disorders (eg, Shwachman-Diamond syndrome, cystic fibrosis), in the vast majority of patients, it accompanies obesity, advanced age, diabetes, and fatty liver.[28–30] The pathophysiologic mechanisms that lead to excess intrapancreatic fat deposition and the clinical and metabolic implications are only beginning to be understood.

The diagnostic criteria for fatty pancreas are subjective and variable. A wide range of techniques have been described for imaging intrapancreatic fat, including trans-abdominal US, CT, MRI, and EUS. On CT, fatty pancreas appears hypodense compared with the spleen. On EUS, a grading system adapted from radiology incorporating the echotexture of the pancreas relative to the spleen as well as the ability to visualize the main pancreatic duct

and “salt and pepper” dots in the parenchyma has been suggested to assess fatty pancreas.[31] MRI is the test of choice for identifying intrapancreatic fat. However, there are little data correlating findings of intrapancreatic fat on EUS or MRI with histology. In addition, the effect of excess intrapancreatic fat on pancreatic exocrine or endocrine function and fibrosis remains unclear. Intrapancreatic fat may have a role in causing or aggravating metabolic, inflammatory, and neoplastic disease processes. Fatty pancreas has been associated with increased severity of acute pancreatitis in the setting of obesity,[32] likely because of proinflammatory cytokine release from injured fat.[33] Some evidence suggests that the proinflammatory milieu induced by obesity contributes to pancreatic oncogenesis through the activation of K-ras signaling pathways.[34] Other important implications of fatty pancreas appear to be its tendency to create background noise that could obscure small solid lesions that would have implications for early detection of pancreatic cancer. Future studies should focus on how to distinguish solid lesions within a fatty pancreas by using EUS.

Research gaps and opportunities

Research should focus on interventions to ensure EUS competence and systematically reduce operator variability in EUS performance. The role of EUS as a diagnostic or prognostic tool for chronic pancreatitis, and whether automation that uses new technology can improve its ability needs to be clarified. Further studies correlating EUS observations with appropriate histologic standards should be conducted as well as the role of tissue acquisition in improving EUS clinical utility. Finally, the epidemiology of fatty pancreas, whether and how fatty pancreas may increase the risk of pancreatic conditions need further study.

Specific priorities include the following: (1) validation of novel competency-based metrics for EUS training; (2) defining the diagnostic and prognostic ability of EUS in chronic pancreatitis by using an appropriate criterion standard such as histology or longitudinal follow-up—such studies should evaluate the incremental value of integrating clinical and laboratory data into EUS performance; (3) establishing a histologic definition for chronic pancreatitis on surgical specimens as well as core biopsy specimens obtained during EUS; (4) evaluating the clinical utility of novel EUS-associated imaging modalities including elastography, digital image analysis, contrast-enhanced imaging, and computer-aided techniques in differentiating PDAC, chronic pancreatitis, and AIP, and reducing interobserver variability; (5) defining EUS criteria for diagnosis of AIP; (6) defining the prevalence of fatty pancreas in the general population and in patients with metabolic syndrome and determining whether the presence of fatty pancreas predicts the presence or risk of cardiovascular disease; (7) establishing the role of intrapancreatic fat in causing inflammation and fibrosis and associated mechanisms; and (8) determining whether fatty pancreas increases the risk and severity of pancreatic diseases, including acute pancreatitis and pancreatic cancer.

EUS IN HIGH-RISK PATIENTS

Overview of the problem

Incidental pancreatic cystic lesions are detected ever more frequently because of increased use of cross-sectional abdominal imaging. The majority of these cysts are mucinous and thus premalignant. Societal guidelines regarding evaluation of pancreatic cysts are controversial and based on little evidence. Formal guidelines for screening and surveying high-risk individuals with familial pancreatic cancer are lacking.

Cystic lesions: The role of EUS, with or without other imaging technologies for differentiating benign and malignant cysts

Once a cyst has been discovered, the patient should undergo MRI with MRCP to better define the cyst and attempt to determine whether it is mucinous or non-mucinous. Mucinous cysts (intraductal papillary mucinous neoplasm [IPMN] and mucinous cystic neoplasms) may warrant further evaluation depending on size and surgical candidacy. The accuracy of MRI for detecting mucinous cysts is 71% to 91%, and for malignant cysts it is 73% to 91%.[35,36] EUS imaging is approximately 50% accurate for differentiating mucinous from non-mucinous cysts.[37] It may be superior to MRI for detecting small pancreatic masses and mural nodules, although interobserver agreement remains an issue with only solid component achieving moderately good agreement. Contrast-enhanced EUS may improve the ability to diagnose nodules as well as differentiate malignant and benign nodules. However, EUS imaging alone remains inadequate for cyst diagnosis. This is confirmed by a study demonstrating the superior diagnostic accuracy of the Fukuoka guidelines, which incorporate EUS-FNA cytology results for diagnosing malignant cysts compared with the Sendai guidelines that rely only on imaging features.[38]

Cystic lesions: Cyst fluid analysis in the differentiation of benign and malignant cysts

EUS-FNA of pancreatic cysts enables cyst fluid analysis for diagnostic and prognostic purposes. Cyst fluid cytology is very specific for the diagnosis of a malignant cyst, but it suffers from poor sensitivity because of paucicellular samples. Carcinoembryonic antigen (CEA) measurement in cyst fluid is helpful for the diagnosis of a mucinous cyst, with a cutoff value of 192 ng/mL being 80% accurate,[37] but the CEA level is not predictive of malignancy. Despite inadequate cellularity in most cyst aspirates, DNA and RNA shed into the fluid can be analyzed for mutations. Next-generation sequencing is currently being used, given its increased sensitivity to detect smaller amounts of DNA and its ability to assay multiple genes simultaneously. From a diagnostic standpoint, KRAS is very specific for mucinous cysts (mucinous cystic neoplasms or IPMN), whereas GNAS is specific for IPMN. Mutations in TP53, PIK3CA, and PTEN have been associated with advanced neoplasia (high-grade dysplasia or invasive cancer) in mucinous cysts, with a sensitivity of 91% and specificity of 97%.[39,40]

Other biomarkers showing promise for diagnosing advanced neoplasia include telomerase, microRNA, mucin profiling, and monoclonal antibody (mAb Das-1).

New EUS-guided technologies for diagnosis of cystic lesions

Needle-based confocal endomicroscopy enables real-time optical biopsies and provides in vivo histopathologic assessment during EUS-FNA via a 19-gauge needle.[41] Serous cystadenomas have been the best studied thus far, demonstrating a typical superficial vascular network, whereas IPMNs exhibit papillary projections with an epithelial border and vascular core.[42] However, the role of confocal endomicroscopy for the diagnosis of pancreatic cysts has not been well established. Recently, a microforceps has been developed for tissue acquisition from pancreatic cystic lesions. During EUS-FNA, the micro-forceps is introduced through the 19-gauge needle, and pinch biopsies are obtained from the cyst wall, septations and nodules, or adjacent masses. In a preliminary study, the tissue acquisition yield was 90%, and microforceps histology was superior to EUS-FNA cytology, especially for providing a specific pancreatic cyst diagnosis.[43] This technology is expected to grow in the future, in which real histology could replace cytology, CEA level measurement, and diagnostic biomarkers.

The role of EUS in screening for familial pancreatic cancer

The goal of pancreatic cancer screening is to detect early cancer and its precursor lesions in individuals with inherited genetic susceptibility leading to an increased risk for developing pancreatic cancer. These high-risk individuals are defined as either having a family history of pancreatic cancer, which includes having at least 2 affected first-degree relatives, or a pancreatic cancer-associated genetic syndrome such as Peutz-Jeghers or Lynch syndrome. MRI and EUS are suggested as preferred imaging modalities in the hope of detecting asymptomatic cancer or high-grade precursor neoplasms (pancreatic intraepithelial neoplasms [PanIN-3] or high-grade branch duct IPMNs). Prospective screening in this high-risk population by using MRI and EUS detects pancreatic lesions in 6% to 42% of patients,[44,45] with an 8.2% yield for detecting high-grade lesions or incidental cancer.[46] Many questions still remain regarding the optimal method and interval for screening and surveillance as well as indications for surgical resection.

Research gaps and opportunities

Future research efforts should focus on enhanced cyst imaging, cyst fluid biomarkers, and EUS-guided technology to allow differentiation of benign and malignant pancreatic cystic lesions and detection of precursor lesions in high-risk individuals. Critical areas of research include the following: (1) new radiologic and EUS imaging technology to improve differentiation of benign and malignant pancreatic cysts, (2) long-term natural history studies of pancreatic cystic lesions, (3) a pancreatic cyst consortium that includes a larger surgically confirmed cohort and a longer observation period to perform cyst fluid and tissue biomarker studies and validation studies, (4) determination of the diagnostic yield of microforcep biopsies compared with confocal endomicroscopy and standard FNA and/or cyst fluid studies for the diagnosis of pancreatic cysts, (5) development of new tissue acquisition devices for pancreatic cysts, (6) development and validation of selection criteria for surgical resection in high-risk individuals, and (7) definition of the optimal method and interval for screening and surveillance in high-risk individuals.

EUS-GUIDED DIAGNOSTICS AND THERAPEUTICS

Overview of the problem

Although EUS is the preferred method of obtaining tissue for diagnosis of pancreatic diseases, and it has become an integral part of patient management as neoadjuvant therapies for locally advanced PDACs have evolved, the best technique to optimize diagnostic yield remains unclear. Beyond diagnostics, EUS has entered therapeutics in which key issues remain regarding lack of appropriate equipment and accessories needed to perform these procedures as well as the need to standardize and improve our current techniques for endoscopic necrosectomy, EUS-guided pancreatic duct access, and EUS-guided ablative therapies.

EUS-guided tissue acquisition: endoscopic and pathology considerations

Typically, diagnosis of PDAC has been obtained by using EUS-FNA cytology, which is highly accurate, although the advent of newer-generation needles for EUS-guided fine-needle biopsy has enabled relatively easy and safe core biopsy of the pancreas. At least 13 different equipment and operator variables may impact the diagnostic yield of EUS-guided tissue acquisition: needle size, needle type, specimen handling and processing, presence of rapid on-site evaluation, number of passes, number of to and fro movements, fanning, central versus peripheral sampling, speed of needle throw, amount and type of suction applied, wet versus dry needle, and operator experience. The optimal combination of these factors has not been identified. Overall, data do not currently support improved diagnostic yield with 25-gauge versus 22-gauge FNA needles, and advantages of the older reverse side–bevel core biopsy needles compared with standard FNA needles remains unclear, other than a likely decreased number of passes needed for diagnosis; suction does appear to improve diagnostic accuracy.[47–49] Rapid on-site evaluation of EUS-FNA specimens enhances diagnostic yield by determining when an adequate tissue sample has been obtained. However, rapid on-site evaluation remains expensive, time consuming, unavailable in large parts of the world, and is comparable to performing 7 FNA passes into solid pancreatic masses.[50] Other methods of determining adequacy such as macroscopic on-site evaluation require study.

Core biopsy specimens may be required for diagnosis of autoimmune pancreatitis, pancreatic lymphoma, and unusual neoplasms such as acinar cell carcinoma. Molecular tissue analysis currently guides individualized therapy of many forms of cancer, and it will become increasingly relevant to management of PDAC in the near future.[51] It is currently unclear which tissue acquisition method will most reliably yield adequate tumor DNA suitable for molecular analysis.

EUS-guided drainage of pseudocysts and walled-off necrosis

Drainage of symptomatic pancreatic pseudocysts and walled-off necrosis (WON) is now typically performed under EUS guidance, which affords increased technical success rates with fewer adverse events than traditional endoscopic transmural drainage techniques.[52] Endoscopic treatment of WON results in better patient outcomes compared with surgery as well as an initial percutaneous catheter drainage approach, and it has rapidly become the

preferred initial treatment.[53,54] Although pseudocysts typically respond well to current management techniques, treatment of WON may require multiple endoscopic interventions and a prolonged treatment course with suboptimal complication rates (morbidity reported as high as 26% and mortality up to 7.5%).[55,56] This likely reflects considerable variability in performance of the procedure. Multiple patient and technical factors may affect outcomes of endoscopic WON treatment, including age, size, and morphology of the collection, creation of 1 versus multiple drainage sites, choice of stents, choice of lavage solution, use of acid suppressive therapies, and degree of necrosectomy performed. A standardized approach to performing endoscopic necrosectomy recently demonstrated high success rates, with 98.3% of patients requiring only 1 treatment session and 3.3% morbidity with no mortality.[56] The use of LAMSs for drainage of WON has improved the ease and technical success of endoscopic drainage, however, retrospective studies have suggested discrepant results when comparing LAMSs to plastic stents.[15–18] LAMSs have introduced new concerns, including formation of stent-related pseudoaneurysms and segregation of remote areas of WON after rapid collapse of the central cavity drained by a LAMS. In order to address the relatively high adverse event rate and mortality risk associated with endoscopic necrosectomy, each component of the procedure should be analyzed to optimize efficiency and safety. Methods regarding access, debridement, lavage, drainage, pancreatic stenting, and nasocystic drainage must be rigorously evaluated. Other aspects of care such as timing of the initial procedure, medication use, and follow-up strategy also must be evaluated with an attempt at standardization.

EUS-guided pancreatic duct access

EUS-guided pancreatic duct access is performed to facilitate stenting of obstructed pancreatic ducts not accessible by ERCP. The pancreatic duct is punctured with a 19-gauge or 22-gauge needle from the stomach or duodenum under EUS guidance. Several variations in this procedure have been described, including passage of a guidewire via the EUS needle across the ductal obstruction, with subsequent ERCP performed over the guidewire (rendezvous procedure), and EUS-guided transmural antegrade placement of stents into the pancreatic duct.[57] The technique can successfully facilitate endoscopic treatment of pancreatic duct obstruction in about 69% to 90% of patients who might otherwise require surgical pancreatic resection. However, significant adverse events are seen in 14% to 60% of patients. Techniques and accessories require further development and refinement to reduce adverse event rates and improve success. At present, these procedures should be performed only by highly experienced interventional endosonographers at tertiary-care centers.

EUS-guided ablation of cysts and tumors

Endoscopic ablation of solid and cystic pancreatic neoplasms has been investigated for over 15 years, but with some exceptions, it has yet to become a standard of care. Modalities that ablate any tissue (including ethanol and radiofrequency ablation) and those that selectively target neoplastic cells (such as paclitaxel injection and photodynamic therapy) have been studied. Multiple phase 1 studies as well as 1 phase 3 trial of EUS-guided fine-needle injection therapies of PDAC have demonstrated the safety of these techniques but have failed to show a survival advantage.[58] Case series suggest that EUS-guided ethanol injection of

functional pancreatic neuroendocrine tumors effectively treats symptoms caused by these tumors.[59]

Ablation of cystic neoplasms by EUS-fine-needle injection has shown promise, with sequential ethanol and paclitaxel injection demonstrating cyst resolution in two-thirds of treated cysts compared with only about one-third resolution after ethanol ablation alone.[60] However, studies have relied on surrogate endpoints, mainly change in cyst volume, rather than assessing cancer prevention, and the risk-benefit ratio of these interventions is unclear, with reported pancreatitis rates up to 10%.

Research gaps and opportunities

Research gaps and opportunities include the following: (1) create a multicenter EUS-FNA/fine-needle biopsy registry to determine optimal methods of EUS-guided pancreatic tissue sampling and the impact of these methods on patient outcomes; (2) assess methods of EUS-guided sampling for optimal DNA recovery and molecular characterization of pancreatic cancer tissue; (3) develop ex vivo models that accurately predict clinical performance of novel EUS tissue acquisition devices; (4) develop methods that improve the efficiency, safety, and cost in EUS-guided tissue acquisition (such as macroscopic on-site evaluation); (5) develop and complete prospective multicenter randomized trials of endoscopic treatment of WON, evaluating various aspects of technique (for example, LAMSs vs plastic stents) as well as timing of procedure and follow-up; (6) determine best approaches to evaluation and management of disconnected pancreatic duct syndrome in patients with pancreatic necrosis; (7) develop novel endoscopic devices and techniques for endoscopic drainage and debridement of WON, EUS-guided pancreatic duct access and stent placement, and ablation of pancreatic cystic and solid neoplasms; (8) assess the impact of local ablative therapies on the biology, stage, and treatment responsiveness of PDAC; (9) develop and validate surrogate endpoints for prevention of malignancy in pancreatic cystic neoplasms, possibly including biomarkers of advanced neoplasia; and (10) assess promising EUS-guided ablative methods in prospective, multi-center, adequately powered studies evaluating clinically important endpoints.

EUS AND NEW TECHNOLOGIES

Overview of the problem

The interpretation of EUS images requires expertise, and there is a high rate of variance between endosonographers. To overcome these limitations, several image-enhancement techniques, such as contrast-enhanced EUS (CE-EUS), elastography, and digital image analysis have been developed recently. More experimental techniques to improve EUS imaging and diagnosis of malignancy, including molecular imaging by using microbubbles and photoacoustic imaging, hold promise but require further refinement and study in humans, whereas the detection of portal venous circulating tumor cells via EUS-FNA may allow more accurate staging and management of patients with PDAC.

Can CE-EUS, elastography, and digital imaging analysis differentiate solid lesions of the pancreas?

CE-EUS uses the unique characteristics of the interaction of gas-filled microbubbles injected intravascularly with US energy to image vascularized structures. There are several types of microbubble-based US contrast agents (UCAs) with different features, which remain unavailable in the United States. The first-generation UCAs were used to perform CE-EUS, whereas second-generation UCAs are used with dedicated contrast harmonic algorithms in EUS. CE-EUS is the generic term that encompasses all contrast-enhanced techniques involved with EUS, whereas contrast harmonic EUS and contrast-enhanced harmonic EUS refer to low mechanical index techniques used in CE-EUS. A typical heterogeneous hypo-enhanced sonographic pattern strongly suggests malignancy, although chronic pancreatitis with severe fibrosis produces a similar pattern. Hyperenhancement or iso-enhancement has strong negative predictive value for pancreatic cancer.[61] Reviews of the utility of UCAs for the diagnosis of PDAC reported promising results.[61,62] The addition of CE-EUS to EUS tissue acquisition may improve the diagnostic accuracy of pancreatic masses and help target areas for biopsy. Recent developments include tumor-specific UCAs with antibodies to specific entities such as CA 19–9 and nanobubbles, which unlike microbubbles, can leave the vascular space and penetrate tumor tissue. Both of these advancements may increase tumor sensitivity and are areas of active investigation.

EUS elastography is an imaging technique that displays in color the differences in tissue hardness, thus estimating elasticity distribution in normal and target areas. For quantitative analysis, the strain ratio, which numerically expresses elasticity in the target area relative to a reference soft tissue area, is used. However, a meta-analysis showed low pooled specificity of 67% for the diagnosis of solid pancreatic masses, suggesting difficulties in the setting of severe fibrosis.[63] Therefore, computer-assisted technology will likely be needed to improve accuracy.

Digital image analysis has been developed to improve diagnostic accuracy and shorten the interpretation process. This is a method to quantify and analyze image information by mathematic or statistical methods by using artificial intelligence with learning algorithms such as artificial neural networks or support vector machines. Digital image analysis can increase the diagnostic rate of not only B-mode but also CE-EUS or elastography.[64,65] Further development of digital image analysis requires randomized multicenter trials, a data registry to enable data mining, and the development of user-friendly programs that can be incorporated into clinical care.

US-guided microbubble techniques for molecular imaging and drug delivery

Molecular imaging by using US builds on the technique of CE-EUS by using ligands attached to the surface of the microbubble that have affinity for specific endothelial molecular targets.[66,67] By attaching ligands such as antibodies to the surface of gas-filled microbubbles, foci of abnormal endothelium can be imaged by using US. In a genetic mouse model of pancreatic cancer, Pysz et al[68] demonstrated the ability of microbubbles that target vascular endothelial growth factor type 2 receptors to enhance the signal of small foci of pancreatic cancer by 27-fold. This study demonstrated the feasibility of performing

molecular imaging by using US. Proteomic analysis identified thymocyte differentiation antigen 1, a marker of neovasculature in human PDAC. UCAs labeled with anti-human thymocyte differentiation antigen 1 antibody demonstrated an increased US signal in mice with pancreatic cancer compared with mice with chronic pancreatitis and wild-type controls.[69] Although this has yet to be tested in humans for detection of PDAC, it has been demonstrated to be safe and feasible in patients with both breast and ovarian lesions.[70]

Microbubbles also can be used to enhance drug delivery in a targeted fashion.[71] Various mechanisms have been investigated for US-enhanced drug delivery including sonoporation, intravascular cavitation, extravascular cavitation, and the use of temperature-sensitive liposomes. Microbubbles in an US field can disrupt cell membranes and endothelial gap junctions, and microbubble cavitation can release drugs that are loaded into liposomes coadministered intravascularly. US that is delivered at sufficient peak-negative pressures can cause tissue destruction without the need for administered microbubbles. This has the benefit of being able to disrupt the stromal matrix in pancreatic tumors, without disrupting the vasculature, enhancing the ability of drug to penetrate into tumors.[72] Lastly, US can be used to create local hyperthermia, allowing for drug-loaded temperature-sensitive liposomes or other photosensitizers to release their payload within a targeted region.[73] Clinical translation of these methods awaits the development of a high-intensity focused US endoscope.[74]

Photoacoustic imaging of the pancreas—lessons learned from other malignancies

Photoacoustic imaging of targeted biomarkers is a promising technique for noninvasive molecular imaging to accurately diagnose and stage pancreatic tumors. Photoacoustic imaging or optoacoustic technology is a state-of-the-art medical imaging modality that provides quantitative optical contrast by using energy conversion from absorbed short-pulse light energy to acoustic waves in the tissue.[75] With the aid of photoacoustic imaging optical contrast agents that bind to diagnostic and prognostic biomarkers of pancreatic cancer, photoacoustic imaging holds great potential as a noninvasive imaging tool that will enable visualization of clinically important pathologic changes at early stages of tumor development.[76] Combined with conventional EUS by adding a laser light delivery system, photoacoustic imaging can provide anatomic and functional information for more reliably differentiating and staging a tumor.

The current endoscopic photoacoustic device used in animal studies needs to be adapted for clinical applications.[77] Although technical concerns with endoscopic photoacoustic imaging due to light attenuation are significant, the most challenging obstacle to imaging a large portion of pancreas will be how to deliver enough laser power through an optical fiber. For photoacoustic imaging to visualize biomarkers of PDAC, molecular probes must be developed and evaluated for extravasation, binding efficiency, excretion, and toxicity.[78] Early stage preclinical applications in pancreatic cancer animal models support the value of photoacoustic imaging for early detection of PDAC,[79] pending further development of operational and visualization techniques.

EUS-guided aspiration of portal venous circulating pancreatic tumor cells

The fact that tumor cells intravasate into the vascular system and appear in the peripheral blood has been known for over 100 years, but techniques to reliably capture and identify circulating tumor cells (CTCs) have been developed only since 2000.[80] CTC analysis requires cell capture and cell detection systems to concentrate the CTC sample, because there is roughly 1 CTC for every 10^7 circulating blood cells.[81] The number of CTCs is low in early stage disease and, until recently, has been thought to be too low to contribute to the detection and assessment of upper GI tract malignancies including PDAC. In 2004, Allard et al[82] were able to detect CTCs in 6 of 16 patients with PDAC, and subsequent refinements in cell capture technologies have resulted in a growing number of observations including the finding that circulating pancreatic epithelial cells can be detected in the presence of premalignant cystic disease.[83]

Pancreatic venous effluent in the portal venous system is an obvious potential source of large numbers of CTCs in PDAC, and in 2015, Catenacci et al[84] demonstrated that EUS-guided transhepatic aspiration of portal venous blood was safe and yielded relatively large numbers (w100 CTCs per 7.5 mL blood) of PDAC CTCs. Further, these CTCs contained the same mutations as seen in regional lymph nodes of patients who later underwent surgery. Subsequently, this group reported that the number of portal vein CTCs (PVCTCs) correlated with the metastatic status of the PDAC.[85] This predictive or stage-confirming utility of the analysis of PV-CTCs has been confirmed by others.[86,87] EUS-guided capture of PV-CTCs may allow early detection of PDAC, guide treatment strategies, and enable further understanding of the biology of PDAC.

Research gaps and opportunities

These technical advances in EUS-guided detection and treatment technologies require further development and validation. Specific research priorities include the following: (1) clinical trials of contrast-enhanced EUS for the discrimination of benign and malignant disease; (2) further development of US contrast agents that are tissue-specific or cell-specific; (3) studies that combine digital imaging analysis with standard EUS, contrast-enhanced EUS, and elastography in patients with benign and malignant disease; (4) further development of safety studies to support U.S. Food and Drug Administration approval of molecular markers of PDAC to allow clinical studies of EUS microbubble methods for PDAC diagnosis and cell-directed therapy; (5) development of a clinically useful high-intensity focused US endoscope; (6) development of a clinically useful endoscopic photoacoustic delivery system; and (7) prospective clinical studies to assess the value of PV-CTC capture and analysis for PDAC staging and clinical management, and standardization of CTC isolation and enrichment platforms with validation studies.

CONCLUSIONS

This workshop addressed the research gaps and opportunities in the field of pancreatic EUS. Diagnostic and therapeutic EUS as applied to both benign and malignant diseases of the pancreas has vastly expanded over the last 40 years. Further advances will be possible only through the interdisciplinary and multicenter collaboration of endosonographers, clinical

pancreatologists, biomedical engineers, and laboratory scientists. Priority areas for research focus on the following 3 areas: improved methodology of specimen acquisition and molecular testing, especially given the rapid growth of personalized medicine; advances in sonographic technology and intravenous agents to enable accurate differentiation of benign and malignant pancreatic neoplasms by using EUS; and development of novel and specialized accessories to make therapeutic EUS procedures safer and more effective. There is clearly a need for consortia for clinical trials as well as biospecimen collection and processing. These efforts will hopefully translate into better and discriminating use of pancreatic EUS.

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Abbreviations:

AIP	autoimmune pancreatitis
CEA	carcinoembryonic antigen
CE-EUS	contrast-enhanced EUS
CTC	circulating tumor cell
EUS-FNA	EUS-guided FNA
IPMN	intraductal papillary mucinous neoplasm
LAMS	lumen-apposing metal stent
MRI	magnetic resonance imaging
PDAC	pancreatic ductal adenocarcinoma
PV-CTC	portal vein circulating tumor cell
UCA	ultrasound contrast agent
WON	walled-off necrosis

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