Perspective

Endoscopic ultrasound comes of age: Mature, established, creative and here to stay!

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ABSTRACT

Research in endoscopic ultrasound (EUS) is alive and kicking! This paper will present recent interesting developments in EUS based on research presented at the Digestive Disease Week (DDW) held in Chicago in 2014. Endosonographers are looking at various techniques to improve yield of fine needle aspiration and core biopsies, assess circulating tumor cells, apply EUS for personalized medicine and develop devices to ensure the adequacy of sampling. EUS may open new vistas in understanding of neurogastroenterology and gastrointestinal motility disorders as discussed in this paper. EUS guided drainage of pancreatic fluid collections, bile duct and gallbladder is feasible, and many randomized trials are being done to compare different techniques. EUS guided delivery of fiducials, drugs, coils or chemo loaded beads in possible. EUS has come off age, has matured and is here to stay! The DDW in 2014 in Chicago was a very active year for EUS. There were numerous papers on different aspects of EUS, some perfecting and improving old techniques, others dealing with randomized trials and many with novel concepts. In this paper, I will highlight some of the papers that were presented. It is not possible to discuss all the abstracts in detail. I have, therefore, chosen selected papers in different aspects of EUS to give the readers a flavor of the kind of research that was presented at DDW.

Key words: Biliary drainage, botulinum toxin, celiac plexus block, chemoembolization, cholecystitis, circulating tumor cells, core biopsies, electroaccupuncture, endoscopic ultrasound, endosonography, fiducials, fine-needle aspiration, gastroparesis, genomics, gastrointestinal stromal tumor, image-guided radiation therapy, motility disorders, needle confocal laser endomicroscopy, neurogastroenterology, pancreatic cancer, pancreatic fluid collection, personalized medicine, ProCore, proteomics, radiation therapy, subepithelial tumor

ENDOSCOPIC ULTRASOUND GUIDED FINE NEEDLE ASPIRATION

Wet suction

There were numerous papers on different aspects of endoscopic ultrasound (EUS) guided fine-needle aspiration (FNA) studying suction or no suction, slow pull or capillary technique, presence or absence of cytopathologist, etc. A relatively new concept that was presented was the concept of wet suction. Applying suction with a syringe during EUS-FNA relies on negative pressure suction in an empty needle after the stylet is removed (dry technique). As water is a less compressible fluid when compared to air, Berzosa *et al.*[1] hypothesized that the volume of vacuum enforced to the distal tip of the needle could be enhanced when the EUS needle is filled with a continuous column of water (wet technique). Using a three-dimensional computational fluid dynamic model they showed that the needle filled with water aspirated the tissue for a much longer distance than the needle filled with air

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for the same simulation time of 0.1 s with the volume of tissue aspirated being about 70% greater in the wet technique when compared to the dry technique. Greater suction ability may lead to more specimens, but also more contamination with blood making interpretation difficult. Therefore, clinical evaluation of this technique will be important and discussed below are a couple of studies that did that.

Attam *et al.*[2] presented a prospective, randomized study of wet versus dry EUS-FNA of solid pancreatic lesions with 22G needles (Cook ProCore or Olympus). Wet technique involved flushing the needle with 5 cc of saline to replace the column of air with saline. The needle was then passed into the lesion, suction applied at maximal strength, needle moved back and forth. Wet suction yielded significantly higher cellularity in cell block with compared to the dry technique, with a mean cellularity of 1.83 (±0.79) versus 1.44 (±0.769) ($P < 0.001$). Wet technique cell block resulted in a significantly better diagnostic yield of 85.5% versus 74.4% ($P < 0.0001$). There was no difference in the amount of hemorrhage.

Berzosa *et al.*[3] compared wet suction, dry suction and a hybrid technique for EUS-FNA. In dry technique, the stylet was removed after puncturing the lesion and continuous negative suction was applied with a 10 cc prevacuum syringe, and the needle moved to and fro. In the wet technique before puncturing the lesion, the stylet was removed, and the needle was preflushed with normal saline. A 10 cc prefilled syringe (3 mL normal saline) was left attached to the proximal port and later used for aspiration after puncturing the lesion. The needle was moved to and fro followed by suction. In the hybrid technique, the needle was prepared as in the wet technique, but suction was applied the same way as in the dry technique. No on-site cytopathology assessment was performed. There was no significant difference between hybrid, wet, and dry techniques in sample adequacy. For total volume aspirate, both hybrid ($P = 0.046$; 95% confidence interval [CI] [0.29, 3.04]) and wet (P = nonsignificant [NS]; 95% CI [−0.1, 2.9]) techniques provided more tissue aspirate (1.5 ± 0.75 mL and 1.4 ± 0.75 mL, respectively) over the dry technique, but only the hybrid was significant. For the diagnostic yield, there was no statistical significant difference between techniques. In 5 lesions either hybrid (4/5) or wet (3/5) provided an adequate sample that made a final diagnosis when dry did not. The authors concluded that for EUS-FNA of solid lesions, the hybrid technique provided a larger amount of volume aspirate when compared to the dry technique. For both sample adequacy and final diagnosis, there was a NS tendency in favor of flushing the needle with normal saline (hybrid and wet) when compared to a standard (dry) technique. The authors did state that this was an underpowered pilot study.

Device to check endoscopic ultrasound-fine needle aspiration sample

Frequently during EUS-FNA there is blood contamination, and it can be difficult to determine whether adequate sample has been obtained for cytological examination. If a cytopathologist is not present onsite, then the problem becomes even more significant. Matsumoto *et al.*[4] developed a device that detects the target specimens within pancreatic tumor EUS-FNA samples. Different single wavelengths of light-emitting diode light were shone onto EUS-FNA samples of dog pancreas to identify the optimum wavelength absorbed specifically by blood covering the target specimen. The device equipped with the optimum wavelength, and named target sample check illuminator (TSCI) was then tested in EUS-FNA. Samples of EUS-FNA were observed by TSCI to determine whether the presence of target specimens could be confirmed. In the canine experiments, the areas with target specimens appeared orange, and those without appeared dark brown under TSCI. In the human EUS-FNA samples, the mean number of needle punctures was 2.4 (range, 1-5), and the agreement rate between TSCI and histopathology in 142 samples was 93.7% (133/142). If this device is validated further and commercially available, it could be very useful in my opinion in ensuring sample adequacy during EUS-FNA and EUS guided core biopsies. The TSCI may be even more important for core biopsies as no onsite pathology evaluation is done of the core biopsies that are sent to histopathology lab in formalin. Sometime only blood elements are found in the core biopsies, and it is visually difficult to determine if there is indeed a tissue core within a blood clot.

Tumor seeding from endoscopic ultrasound-fine needle aspiration

Ngamruengphong *et al.*[5] tried to study the potential effect of tumor seeding after EUS-FNA in respectable pancreatic cancer on survival using the data from the linked Surveillance, Epidemiology, and End Results data. They identified all patients aged 66 years or older with pancreatic cancer between 1998 and 2009 and included

patients with locoregional cancer who underwent curative intent surgery in 2034 patients: 498 (24%) in EUS-FNA group and 1536 (76%) in non-EUS-FNA group [197 underwent EUS without FNA; 1339 did not receive EUS]. In unadjusted analysis, median overall survival was 22 months (95% CI 19-25) in EUS-FNA group versus 15 months in non-EUS-FNA group (95% CI 14-16). Median pancreatic cancer-specific survival was 24 months (95% CI 20-27) vs 18 months in non-EUS-FNA group (95% CI 16-19). In a multivariate analysis after controlling for other covariates, EUS-FNA was not associated with an increased overall mortality (hazard ratio [HR] 0.85; 95% CI 0.73-1.00) or pancreatic cancer mortality (HR 1.13; 95% CI 0.94-1.37).

ENDOSCOPIC ULTRASOUND GUIDED TISSUE AND CORE BIOPSY

Comparison of core biopsy needles

It is becoming increasingly important in many scenarios to get a large core biopsy during EUS. For many years a 19G Quick-Core needle (Cook Medical, Inc.) has been available that was in my opinion stiff, complex to operate, cumbersome to use and not very popular with most endosonographers. Dewitt *et al.*[6] compared the technical success, diagnostic histology, accuracy and complication rates of a new 19-gauge EUS histology needle (ProCore® (PC), Cook Medical Inc., Winston-Salem, NC) to the conventional needle (19G, Quick-Core® (QC), Cook Medical) for histologic diagnosis. Patients at two hospitals presenting for EUS and possible histologic biopsies were enrolled. ProCore specimens had a higher frequency of diagnostic histology (85% vs. 57%; $P = 0.006$), accuracy (88% vs. 62%; $P = 0.02$), mean total length (19.4 vs. 4.3 mm; $P = 0.001$), mean complete portal triads from liver biopsies (10.4 vs. 1.3; $P = 0.0004$) and required fewer crossover biopsies (2% vs. 65%; $P = 0.0001$). The authors concluded that biopsy specimens from the 19G ProCore needle have a higher frequency of diagnostic histology, accuracy and specimen length, but similar overall technical success and complication rate compared with the 19G Quick-Core needle.

Core biopsy of muscularis propria

Gastroparesis is a very challenging disease to treat and investigate. Biopsies of the muscularis propria in gastroparetic patients generally require surgical full thickness biopsies (FTB) for staining for loss of Interstitial Cell of Cajal (ICC) in the MP, inflammatory changes and neuronal loss in the myenteric plexus. Othman *et al.*[7] investigated EUS guided core biopsies of the stomach wall in gastroparetics and compared the tissue to a surgically obtained FTB in the same patient in a feasibility trial in 9 patients who were undergoing gastric neurostimulator placement. EUS guided biopsy of muscularis prorpia was done with a 19 gauge core needle in the antrum utilizing up to 5 passes. Endoscopic and surgical specimens were compared for tissue morphology, count of ICC (c the-kit stain), enteric neurons (S100 stain) and fibrosis (trichome). EUS guided core biopsies obtained sufficient tissue for histological assessment of ICC in 8 patients (88%) and for the myenteric plexus in 5 patients. There was a high-correlation coefficient (0.73) when comparing both surgical and endoscopic groups for the loss of ICC. No postprocedure complications were reported. This minimally invasive approach could replace surgical FTB in these patients with the potential to have much better understanding of the pathophysiology of these patients that may assist in develop targeted therapies for gastroparesis.

Endoscopic ultrasound guided through the needle biopsy and tunneling biopsy

Nakai *et al.*[8] studied the use of an EUS guided through the needle biopsy (EUS-TTNB) using a miniature biopsy forceps that could be passed through a 19G EUS-FNA needle. A total of 14 cases (12 pancreatic and 2 nonpancreatic) underwent 15 sessions (12 initial sessions and 3 sessions after nondiagnostic EUS-FNA) and 36 passes of EUS-TTNB between December 2012 and October 2013. The median diameter was 30 mm. The final diagnoses were 5 adenocarcinoma, 4 AIP, 1 sarcoma, 1 pNET, 1 gastrointestinal stromal tumor (GIST), 1 schwannoma, 1 necrotic tumor. Puncture was technically successful in all cases (12 transgastric and 2 transduodenal). Macroscopic histologic core by EUS-TTNB was obtained in 61% per pass; tissue acquisition rate by EUS-TTNB alone was 61%/pass and 100%/ session. When EUS-TTNB and subsequent EUS-FNA were combined, tissue acquisition rate was 92%. The authors concluded that EUS-TTNB was safe and technically feasible and provided an additional tissue acquisition technique.

Wang *et al.*[9] on the other hand took a different approach to obtain pathological specimens of subepithelial masses by EUS-guided "deep tunneling" forceps biopsy technique in eleven cases (three cases of esophageal and eight cases of gastric subepithelial lesions). The abnormal esophageal and gastric

subepithelial lesions were punctured under EUS guidance with a 1.8 mm diameter biopsy forceps introduced through the biopsy channel. Biopsy forceps was then directly punctured into the mass and specimens were grasped with the biopsy forceps. In the event that the mucosa could not be punctured, the biopsy forceps was used to breach the mucosal layer and "tunneled" into the subepithelial lesion under EUS monitoring. Adequate tissue was obtained for histopathological examination in all eleven cases. There were two cases of poorly differentiated adenocarcinoma, five cases of signet ring cell carcinoma and one case of lymphoma. There were also two cases of inflammatory esophageal lesions and one case of esophageal adenocarcinoma. No complications occurred.

MOLECULAR AND OTHER MARKERS ON CYTOLOGY/HISTOLOGY OBTAINED BY ENDOSCOPIC ULTRASOUND

An emerging and very important aspect of cancer medicine is the development of personalized medicine with the explosion of genomics, proteomics and various molecular markers being done on cancer tissue. This is already being applied for many cancers resulting in dramatic treatment responses (e.g., melanoma) and developing an individual treatment plan for each cancer patient based on their personalized molecular and genetic profile, with the knowledge of prognosis as well as information on which treatments the individual patient will or will not respond to. Many papers were presented at Digestive Disease Week (DDW) on studying these kinds of markers on EUS-FNA and core biopsies. This concept will be important for developing and applying tumor specific targeted therapies in individual patients.

Nguyen *et al*.[10] evaluated the feasibility of S100A2 and S100A4 assessment in EUS guided biopsy specimens using the 22 G ProCore needle and evaluated the relationship of these biomarkers with outcome in the patient with pancreatic adenocarcinoma. Sections of cell-block material were assessed for S100A2 and S100A4 protein expression using immunohistochemistry with biomarker assessment from EUS acquired specimens was possible in 91% (112/123) of patients. S100A2 and/or S100A4 were expressed in 57 (50%) patients, and were co-expressed in 97% of cases. Pancreatectomy was performed in 24 (20%) patients, and concordant rate of S100 biomarkers staining between surgical and EUS specimens were 89%. Overall, patients with S100A2/A4+ve cancer on EUS had a significantly shorter median survival (10.0 vs. 17.0 months, $P = 0.004$). Pancreatectomy in patients with S100A2/A4 expressing cancer did not lead to a statistical survival benefit compared with those with nonsurgical management ($n = 46$) (17 vs. 9.5 months, $P = 0.42$).

Benesova *et al*.[11] studied the utility of EUS-FNA and core biopsy samples for DNA and in particular, miRNA testing in of 65 pancreatic cancer patients. KRAS mutations were detected by denaturing capillary electrophoresis, miRNA presence was quantified by real-time PCR of miRNA-specific cDNA obtained by a standard reverse-transcription from total RNA extracted from samples. Several commercial kits were tested for RNA extraction as well as reverse-transcription and real-time quantification of examined miRNAs. For the highest fraction of mutated cells in the sample, the best experimental combination was 22G needle (Cook ProCore or Olympus) for biopsies taken from the pancreatic head and 19G Boston Scientific needles for body and tail biopsies. Proper selection of needle type and absence of aspiration were found to be key in minimizing blood contamination, high yield of extracted material with a high portion coming from mutated (i.e., cancerous) cells.

Gleeson *et al*.[12] studied the frequency of pathogenic alterations within EUS-FNA cytology specimens from malignant lymph nodes (LN), and the presence of one or more alterations associated with existing or experimental targeted therapies in patient with rectal cancer. DNA extraction from 131 of 231 (57%) screened archived malignant LN cytology slides from 2002 to 2010, yielded suitable quantity and quality (55 ng/ul [range, 0-333]) for NGS in 127 (97%) patients. The Ion AmpliSeqTM V2 Cancer Hotspot NGS Cancer Panel and MiSeq sequencers were used to simultaneously sequence and assess for 2,500 possible mutations in 50 key cancer genes. Complete sequencing was achieved in 102 patients' whereby 191 pathogenic alterations were identified in 19 genes. Genotyping revealed mutations in TP53 (35%), APC (22%), KRAS (17%), FBXW7 (5%), PIK3CA (4%), BRAF (3%), SMAD4 (3%) and GNAS (1%). Forty-three percent of LN's harbored at least one pathogenic alteration that has been linked to clinical treatment option or is currently being investigated in new targeted therapy clinical trials.

ENDOSCOPIC ULTRASOUND GUIDED DRAINAGE

Endoscopic ultrasound guided drainage of various ducts, cysts and fluid collections have been reported for many years. This was also a dominant theme at this year's DDW and some of the research in this area of EUS is highlighted below.

Endoscopic ultrasound guided bile duct drainage

Endoscopic ultrasound-guided biliary drainage (EUS-BD) can be performed transgastrically (hepatogastrostomy [HG]) or transduodenally (choledochoduodenostomy [CDS]) without accessing the papilla (direct transluminal technique or TL). Khashab *et al.*[13] compared the efficacy and safety of both techniques in 150 consecutive jaundiced patients with distal malignant biliary at 7 tertiary centers. Clinical success in patients with successfully placed biliary stents was attained in 83.33% patients in CDS group as compared to 81.82% in HG group ($P = 0.82$). Adverse events occurred more commonly in HG group (23.6% vs. 16.4%, $P = 0.28$). Adverse events were more common in patients who underwent plastic stenting as compared to metallic stenting (47% vs. 16%, $P = 0.004$). Length of stay was shorter in CDS group (5.55d vs. 12.71d, $P = 0.0001$). During mean long-term follow-up of 118 + 152.40 days, stent obstruction and/or migration occurred in 9.84% of the CDS group and in 21.34% of the HG group ($P = 0.06$) (time to stent occlusion was significantly longer in the CDS group ($P = 0.009$ by log-rank test). On multivariate analysis, only plastic stenting was independently associated with adverse events (odds ratio 4.1, $P = 0.008$). CDS is associated with shorter hospital stay, longer stent patency and fewer procedure- and stent-related complications. Metallic stents should be placed whenever feasible as plastic stenting is independently associated with the occurrence of adverse events.

Endoscopic ultrasound guided gall bladder drainage

Cholecystitis patients with significant comorbidities have conventionally been offered percutaneous gallbladder drainage (PGD) if they are too sick for cholecystectomy. PGD carries a significant risk of catheter-related complications, patient discomfort, and is contraindicated in selected patients. Kahaleh *et al.*,[14] presented an international collaborative study on EUS-guided gallbladder drainage in three centers with a total of 35 patients undergoing EUS-GLB. Technical success occurred in 91.4% of cases. Immediate adverse events occurred in 11% of patients: Bleeding in 2, stent migration in 1 and hemoperitoneum in 1 requiring surgery. Delayed adverse events occurred in 14% of patients: Abscess in 2 and recurrence of cholecystitis in 3 patients. Long-term clinical success rate was 88.5%, without further intervention. The authors concluded that the endoscopic drainage provided a less invasive method for biliary decompression compared to PGD in high-risk cholecystitis patients. EUS-GLB appeared to be feasible, safe, and effective in patients having failed transcystic stent placement via ERCP. Further prospective studies are needed to confirm these findings.

Endoscopic ultrasound guided drainage of pancreatic fluid collections

Endoscopic ultrasound-guided drainage of pancreatic fluid collections (PFC) is usually performed with fluoroscopy and anesthesia support. In some situations, these may not be available. Schneider *et al.*[15] assessed the short and long-term outcomes of EUS-guided PFC drainage without fluoroscopy or anesthesia support in 80 consecutive patients with symptomatic fluid collections, at least 6 cm, accessible via the stomach or duodenum, and <2 cm from the GI wall. Cysts with estimated >40% debris were excluded unless the patients were septic. EUS was performed under conscious sedation with midazolam (2.5-10 mg) and fentanyl (100-300 μg), without intubation, in the left lateral decubitus position. In all cases, an attempt was to place at least two stents. EUS guided drainage of PFC was successful, 74/80 (93%). Repeat interventions were required in 16/74 (22%) cases. The mean time to re-intervention was 121 ± 197 days (median 30-day). Complications were noted in 9/80 (11%) attempts (2 severe bleeding, 4 free perforations [3 due to punctures of cysts in regions not adherent to the stomach], 1 stent-related pressure ulcer, 1 minor bleed, 1 stent migration). There were no cases of aspiration.

ENDOSCOPIC ULTRASOUND GUIDED INJECTION THERAPY: DRUGS, FIDUCIALS, COILS, BEADS AND WHAT NEXT?

Fiducials

Image-guided radiation therapy (IGRT) is dependent on the presence of fiducial markers for target localization and tracking. EUS-guided placement of fiducial markers has been reported in GI malignancies; however,

assessment of its feasibility and complications remains limited in the literature. Al-Haddad *et al.*[16] prospectively evaluated the feasibility and safety of EUS-guided placement of fiducials in GI malignancies for IGRT in a multicenter setting in pancreatic, esophageal and anorectal cancer. No complications related to fiducial placement were reported on 48 h and 30-day assessments. Pretreatment planning CT was performed within a median of 4-day (range, 2-45) of EUS with adequate visualization of fiducials in all patients except one PDAC patient due to migration and those were not replaced. IGRT was successfully initiated in 41 patients (2 patients had progression of the disease prior to initiation of IGRT) and was completed in 35 (85%; discontinued due to poor tolerance in 4, and disease progression in 2). No significant migration outside the treatment field was noted in any fiducial by the end of IGRT except in one PDAC patient. The authors concluded that EUS guided fiducial placement is safe and feasible in GI malignancies and is associated with high-completion rate of IGRT and low incidence of complications or fiducial migration.

Drugs, coils and beads

Paik *et al.*[17] evaluated the efficacy and safety of EUS-guided ethanol ablation in small solid pancreatic neoplasm in a case series of 8 patients with (2 nonfunctioning neuroendocrine tumors (NETs), 3 insulinomas, 1 gastrinoma and 2 solid pesudopapillary tumors). All enrolled patients were treated with 99% ethanol injection under linear array (EUS) guidance. The mean diameter of the tumor was 14 mm (range, 7-29 mm), and median amount of ethanol injected was 2.8 mL (range, 1.2-10.5 mL). There were 3 mild adverse events after treatment (2 transient abdominal pain and 1self-limiting fever). Severe acute pancreatitis occurred in 1 patient who received EUS-guided ethanol ablation with a 20-gauge CPN needle. The authors concluded that the EUS-guided ablation might be useful and less invasive as a treatment modality for borderline malignant pancreatic neoplasm. However, repeated procedural sessions or surgical intervention may be required if necessary. In addition, procedure-related adverse events must be carefully monitored.

Endoscopic ultrasound-guided celiac plexus block (CPB) is of uncertain value for pain due to chronic pancreatitis (CP), because of the absence of sham-controlled trials. Eisendrath *et al.*[18] presented results of an ongoing study of the first randomized sham-controlled trial of EUS-guided CPB in patients referred to one of 2 tertiary referral centers (1 North American, 1 European) for possible EUS-guided CPB. Randomization was performed by sealed envelope immediately following diagnostic EUS, to either CPB (bilateral injection of 20cc bupivacaine 0.5% + 1 cc triamcinolone [40 mg/cc] with a 19 g FNA needle) or to sham (diagnostic EUS only). Patients were blinded to treatment arm. A single dose of intravenous (IV) antibiotic (or saline) was administered per-procedure. Pain response and pain killer treatment were monitored at 1 and 4 weeks, then monthly for 6 months by a research assistant blinded to treatment arm. 36 patients (median age: 52 (28-71), 23 males) were randomized (18 CPB, 18 sham), 4 CPB were lost to follow-up. Baseline pain data: (1) duration: Median 36 months (9-240); 2) mean VAS severity 7/10 (±1, 3). Mean % pain reduction at 1-month was significantly higher with CPB (−29% ± 46% vs + 1% ± 26%; $P = 0.011$); with no significant change in morphine use (+136% ± 566% vs + 277% ± 402%; $P = 0.169$). Patient recruitment in this trial will continue to 40/arm. The authors concluded that for pain due to CP: CPB reduces pain more than a sham, but with no change in morphine consumption and study completion is required to confirm these findings.

The liver is a common site of distant metastases. While solitary metastases may be treated with a variety of local options, for diffuse hepatic metastases the only current option is systemic chemotherapy. Drug-eluting microbeads have been used for transarterial chemo-embolization of localized disease. Their use in the portal system has not been described. Faigel *et al.*[19] hypothesized that EUS guided Portal Injection of Chemotherapy (EPIC) using irinotecan loaded microbeads may achieve increased intrahepatic concentrations, while decreasing systemic exposure. EPIC was performed using irinotecan-loaded microbeads in the acute nonsurvival porcine model and hepatic, plasma, bone marrow, and skeletal muscle levels were compared to systemic administration of nonloaded irinotecan. Compared to systemic administration, EPIC resulted in almost twice the hepatic concentration of irinotecan and half the systemic concentrations in plasma, bone marrow and skeletal muscle. SN38 levels were lower in all sites with EPIC. Liver histology showed the beads scattered within small portal venules in the liver. The authors concluded that EPIC using irinotecan-loaded microbeads may enhance the hepatic exposure to irinotecan while decreasing systemic concentrations, and it holds promise as a novel therapy for patients with hepatic metastases.

Endoscopic ultrasound-guided angiotherapy is a growing concept which allows for precise delivery of intravascular therapies to afferent vessels and real-time confirmation of thrombosis and hemostasis. Storm *et al.*[20] presented a series of three cases using EUS-guided angiotherapy for management of large gastric varices, large rectal varices and a nonoperative bleeding GIST. Fujii *et al.*[21] also presented a series of 11 patients undergoing EUS-guided variceal therapy to manage choledochal (n = 5), duodenal (n = 3), and endoscopically undetectable gastric (n = 2) or esophagogastric (n = 1) varices. The mean size of the largest targeted varix was 7.4 ± 4 mm. An average of 4.4 ± 1.9 coils was placed during the initial procedure. No adverse events were reported. The authors concluded that EUS-guided coiling of endoscopically undetectable esophagogastric and ectopic varices is safe and feasible in select patients failing conventional therapy and should be considered in the clinical management of these patients.

Hypertensive anal sphincter can lead to sphincter dyssenergia resulting in constipation from rectal outlet obstruction. Despite biofeedback therapy, these patients are difficult to treat. Byrne *et al.*[22] performed EUS guided botulinum toxin (Botox) injection into the internal anal sphincter in 9 patients with anal sphincter dyssynergia. These patients with chronic constipation from hypertensive anal sphincter had failed biofeedback therapy. All patients underwent anorectal manometry before and after Botox injection. Under EUS guidance, 80 units of Botox was injected into the internal anal sphincter using a 22 gauge FNA needle. Symptoms were scored at baseline and on follow-up (6-8 weeks) using a visual analog scale. Anal sphincter pressure decreased in all patients. Eight of 9 patients (89%) had improvement in symptoms of constipation. Defecatory index with balloon expulsion significantly improved after Botox injection. One patient had a single episode of fecal incontinence. The authors concluded that EUS guided Botox injection into the internal anal sphincter is an effective and safe method for treating chronic constipation secondary to anal sphincter dyssynergia. Or I could say, injecting "Botox" into "buttocks" using endoscopic ultra - "sound" may be a "sound" decision!

ADVANCING BASIC UNDERSTANDING OF PHYSIOLOGY AND PATHOBIOLOGY USING ENDOSCOPIC ULTRASOUND

Advancing neurogastroenterology

Gastric enteric nervous system (GENS) consists of the myenteric plexus, mainly regulating muscle activity, and the submucosal plexus, regulating mucosal functions. Dysfunction of GENS results in various motility/functional and could affect mucosal defense. Samarasena *et al.*[23] reported noninvasive, *in vivo* visualization of GENS using EUS guided needle-based confocal laser endomicroscopy (nCLE) (Cellvizio AQ Flex nCLE probe — Mauna Kea Techn., Paris, France), in the porcine stomach with local injection of a neuronal probe NeuroTrace (NT) and expression level and localization of several neuro peptides: CGRP, nerve growth factor (NGF), its receptor TrkA and melatonin receptor (MTR1). EUS guided nCLE imaging visualized neuronal cells, nerve bundles and fibers in distinctive image patterns: Thin strands, thick fibers and branched fibers. Fluorescence microscopy showed that *in vivo* injected NT was retained in GENS. CGRP and NGF were strongly expressed in the majority of neural cells, Schwann cells and nerves. NGF and TrkA were expressed in neural structures, gastric chief cells and vascular endothelial cells. The authors suggest that strong expression of NGF in GENS indicates its important, but previously unrecognized regulatory roles, neuropeptide expression in neural, endothelial, epithelial and ECL cells indicates cross-talk and local interactions between these cells. Strong MTR1 receptor expression in neural and ECL cells indicated circadian regulatory functions. In my opinion, this is a fascinating application of EUS with nCLE that along with ability to get core biopsies of the muscularis propria as discussed earlier[7] could open a new chapter in understanding and further advancing the field of neurogastroenterology to help develop targeted therapies.

Circulating tumor cells

Pancreatic cancer is a leading cause of cancer-related deaths in the US. Circulating tumor cells (CTCs) have been explored as a noninvasive evaluation of tumor burden, prognosis and survival in pancreatic cancer. In general, relatively advanced disease is required before CTC detection is possible in the peripheral blood (PB). Waxman *et al.*[24] reported a Phase I feasibility/safety protocol is to detect CTCs in the portal vein of pancreatic cancer patients acquired via EUS guided FNA in 10 patients with pancreatic cancer. Portal Vein Sampling was done under EUS-guidance, with a 19 G EUS-FNA needle. The sample was transferred to the Veridex Cell Search Kit (Janssen Pharmaceuticals) and submitted for analysis. Detection of CTC's in the portal vein was significantly higher (mean 71.8 CTCs; standard error of the mean [SEM] 28.2) compared

to the PB (Mean 0.3 CTCs; SEM 0.3; $P < 0.05$). No complications were observed. The authors suggested that these findings will open new research opportunities to better risk stratify otherwise respectable pancreatic cancer patients. I believe that this was a very innovative application of EUS to translational medicine and such approaches along with genomic and molecular profiling of pancreatic tissue can hopefully make a dent in the overall dismal prognosis of pancreatic cancer.

COMBINING ANCIENT WISDOM WITH MODERN TECHNOLOGY

Electroacupuncture (EA) has been used as part of Traditional Chinese Medicine for centuries. Teoh *et al*.[25] presented a randomized, double-blind, sham-controlled trial to investigate the efficacy of EA in reducing procedure-related pain and the consumption of analgesics during EUS in 64 patients. EA was applied to acupoints relevant to the treatment of upper abdominal pain and anxiety, including Zusanli (stomach meridian ST-36), Hegu (large intestine meridian LI-4), and Neiguan (pericardium meridian PC-6). Electric stimulation was employed to the needles at a frequency of 2 Hz, pulse width of 200 μs, and stimulation intensity short of discomfort. The primary outcome of the study was the dose of patient-controlled analgesia consumed (propofol and alfentanil). The secondary outcomes of the study included overall pain score, patient satisfaction, the willingness to repeat the procedure, endoscopist satisfaction score, total procedure time, episodes of hypotension, and episodes of desaturation. A scheduled interim analysis was performed when half of the study recruitment was achieved. Patients in the EA group had significantly lower total dosage of propofol requirement ($P < 0.001$), number of PCA demands ($P < 0.001$), overall pain score ($P < 0.001$) and patient satisfaction score ($P = 0.002$). Patients in the electroaccupunture group were also more willing to repeat the procedure ($P = 0.05$). The study was terminated early as the results convincingly showed that the use of EA significantly reduced discomfort during EUS, analgesic requirements and improved patient satisfaction. This study was very interesting and fascinating as alternative/traditional medicine is more and more being integrated into modern allopathic medicine. Just like products like menthol and capsaicin are used as painful counter irritants on the skin to relieve internal pain (for example in joints), using "needles" for electroaccupuncture on the skin may help us in deploying "needles" inside the body to perform EUS and FNA.

In conclusion, EUS has come off age, is not a passing fancy any more as some skeptics had predicted years ago. It has matured as a modality and a clear subspecialty within gastroenterology and endoscopy. Research in EUS is vibrant and alive, EUS is here to stay and no wonder we now have a dedicated journal called EUS which is a Platform of Our Own for all aspects of endosonography. On behalf of the Editors in Chief and the entire editorial team of EUS, I hereby invite authors whose research at DDW was highlighted above to submit original papers for consideration for possible publication (after peer review) in EUS (www.eusjournal.com).

REFERENCES

1. Berzosa M, Uthamaraj S, Dragomir-Daescu D, *et al*. EUS-FNA Wet vs. Dry suction techniques; a proof of concept study on how a column of water enhances tissue aspiration. *Gastrointest Endosc* 2014;79 Suppl:AB421-2.
2. Attam R, Arain MA, Bloechl SJ, *et al*. Wet suction FNA technique: A novel technique for EUS-FNA. Results of a prospective, randomized and blinded study. *Gastrointest Endosc* 2014;79 Suppl:AB110.
3. Berzosa M, Villa N, Bartel MJ, *et al*. Pilot study comparing hybrid vs. Wet vs. Dry suction techniques for EUS-FNA of solid lesions. *Gastrointest Endosc* 2014;79 Suppl:AB430.
4. Matsumoto K, Ueki M, Harada K, *et al*. Development of a device for facilitating the detection of target specimens from EUS-FNA samples in pancreatic tumors. *Gastrointest Endosc* 2014;79 Suppl:AB175.
5. Ngamruengphong S, Swanson KM, Shah N, *et al*. Pre-operative endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) does not affect survival of patients with resected pancreatic cancer. *Gastrointest Endosc* 2014;79 Suppl:AB307-8.
6. DeWitt JM, Lin J, Al-Haddad MA, *et al*. Comparison of EUS-guided tissue acquisition using two different 19-gauge core biopsy needles: A multicenter, prospective, randomized and blinded study. *Gastrointest Endosc* 2014;79 Suppl:AB110.
7. Othman MO, Davis BR, Torabi A, *et al*. Comparison of histological characteristics of the gastric wall muscularis propria in gastroparetic patients by endoscopic ultrasound (EUS) fine needle aspiration (FNA) technique versus full thickness surgical biopsy. *Gastroenterology* 2014;146 Suppl 1:S610-1.
8. Nakai Y, Isayama H, Chang KJ, *et al*. A pilot study of EUS-guided through-the-needle biopsy (EUS-TTNB) of solid masses. *Gastrointest Endosc* 2014;79 Suppl:AB175-6.
9. Wang D, Xie J, Soon TE, *et al*. The diagnostic value of EUS-guided "Tunneling" forces biopsy technique for gastrointestinal sub-mucosal lesions. *Gastrointest Endosc* 2014;79 Suppl:AB432.
10. Nguyen NQ, Ruszkiewicz A, Chang D, *et al*. Biomarker assessment from EUS guided biopsy predicts survival outcomes and surgical treatment in pancreatic carcinoma. *Gastroenterology* 2014;146 Suppl 1:S275.
11. Benesova L, Belsanova B, Cuperkova R, *et al*. EUS-guided biopsies for molecular testing of pancreatic cancer: Optimization of experimental parameters for DNA and miRNA extraction and analysis. *Gastroenterology* 2014;146 Suppl 1:S280.
12. Gleeson FC, Kipp BR, Voss JS, *et al*. EUS FNA cytology mutation profiling using next-generation sequencing: Personalized care for treatment NaïVE locally advanced rectal cancer. *Gastrointest Endosc* 2014;79 Suppl:AB447.
13. Khashab M, Messallam AA, Peñas I, *et al*. International multicenter comparative trial of EUS-guided biliary drainage done by hepatogastrostomy vs. Choledochoduodenostomy approaches in 150 patients. *Gastrointest Endosc* 2014;79 Suppl:AB174-5.

14. Kahaleh M, Artifon EL, Kedia P, *et al*. International collaborative study on EUS-guided gallbladder drainage: Are we ready for prime time? *Gastrointest Endosc* 2014;79 Suppl:AB418-9.
15. Schneider CP, Paquin SC, Sahai A. Feasability, safety, short and long-term outcomes of EUS-guided drainage of pancreatic fluid collections without fluoroscopy or anesthesia support. *Gastrointest Endosc* 2014;79 Suppl:AB414.
16. Al-Haddad MA, Lekkerkerker SJ, DeWitt JM, *et al*. A multi center prospective assessment of the feasibility and safety of EUS guided fiducial placement for gastrointestinal malignancies. *Gastrointest Endosc* 2014;79 Suppl:AB447.
17. Paik WH, Seo DW, Dhir VK, *et al*. EUS-guided ethanol ablation of small solid pancreatic neoplasm. *Gastrointest Endosc* 2014;79 Suppl:AB413.
18. Eisendrath P, Paquin SC, Delhaye M, *et al*. A randomized, double-blinded, multi-center, sham-controlled trial of EUS-guided celiac plexus block for pain due to chronic pancreatitis. *Gastrointest Endosc* 2014;79 Suppl:AB168.
19. Faigel DO, Lake D, Landreth TL, *et al*. Feasibility of EUS-guided portal injection of chemotherapy (EPIC) using irinotecan-loaded microbeads for the treatment of hepatic metastases. *Gastroenterology* 2014;146 Suppl 1: S692-3.
20. Storm AC, Kumbhari V, Saxena P, *et al*. EUS-guided angiotherapy. *Gastrointest Endosc* 2014;80:164-5.
21. Fujii L, Law R, Wong Kee Song LM, *et al*. Endoscopic ultrasound (EUS)-guided coil embolization in the management of esophagogastric and ectopic varices. *Gastrointest Endosc* 2014;79 Suppl:AB508-9.
22. Byrne KR, Glapa A, Khan AH, *et al*. Manometric evaluation of endoscopic ultrasound guided botulinum toxin injection into the internal anal sphincter in patients with anal sphincter dyssynergia. *Gastrointest Endosc* 2014;79 Suppl:AB404.
23. Samarasena JB, Chang KJ, Ahluwalia A, *et al*. Novel insight into gastric enteric nervous system using EUS-guided needle based confocal laser endomicroscopy, neuronal probe and molecular imaging. Evidence for common mediators and cross-talk between neural, endothelial, epithelial and ECL cells. *Gastroenterology* 2014;146 Suppl 1:S121.
24. Waxman I, Koons A, Konda VJ, *et al*. Detection of portal vein (PV) circulating tumor cells (CTCs) in pancreatic cancer (PC) patients obtained by EUS guided Pv sampling. A safety and feasibility trial. *Gastrointest Endosc* 2014;79 Suppl:AB173-4.
25. Teoh AY, Leung WW, Chong C, *et al*. Electroacupuncture analgesia for endoscopic ultrasound: A prospective, randomized, double-blinded, sham-controlled study. *Gastroenterology* 2014;146 Suppl 1:S902.

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