Introduction

Since its inception in the 1980’s, Endoscopic Ultrasound (EUS) has continued to evolve. Over the past decade a variety of new tools have been developed to expand the therapeutic potential of EUS. EUS can now provide access to various fluid collections and different portions of the gastrointestinal tract, provide therapy (either directly or help guide it) for tumors, and provide enhanced imaging capabilities to assist with diagnosis. These new tools and devices can then be delivered through new echoendoscopes with forward viewing capabilities that may facilitate EUS interventional procedures.

I. Access: Stents

1. Lumen Apposing Metal Stents (LAMS)

In the past, EUS-guided transluminal drainage of pancreatic fluid collections, as well as obstructed biliary and pancreatic ducts have been performed using plastic and metal stents originally designed for use with endoscopic retrograde cholangiopancreatography (ERCP). However, there are major drawbacks to using these types of stents which do not allow for lumen apposition to anchor the stent in position, often are too long, and cannot properly seal the apposing lumens. Therefore, complications encountered can include leakage, perforation, tissue damage, and migration. In order to overcome these issues, LAMS were designed specifically for transluminal drainage and appear to have the advantage of easy deployment and the ability to perform endoscopic debridement through them with low rates of migration and other complications. A few other short “flanged metal stents have also been produced but are not widely available with limited published data on their efficacy. Images (Figures 1-2) and descriptions of the stents described below were recently published in Weilert et al.’s review.1

1) Axios Stent

Binmoeller et al. were the first to publish the creation of LAMS for endoscopic drainage in 2011.2 The Axios stent (Xlumena Inc., Mountain View, CA, USA) consists of double-walled flanges with diameters that are double the stent lumen (dumbbell shape) and hold the tissue walls in apposition (Fig. 1). In the U.S.A.,
Currently available stent diameters are 10 mm and 15 mm. The stent design includes nitinol wire and is fully coated to prevent leakage and allow for removal. The large flanges and a short stent length of 10 mm are designed to distribute pressure evenly on the lumenal wall and allow for anastomosis creation. More recently, the 10Fr Axios stent delivery system has been modified to include a cautery tip to facilitate puncture through the GI tract wall (HotAxios) and obviate the need for dilation in order to deploy the stent. This stent has only recently been approved for use in Europe and the U.S.A.

2) Spaxus Stent

The Niti-S Spaxus stent (Taewoong Medical Co., Ltd., Ilsan, Korea) was first described by Moon JH et al., and is another LAMS with similarities to the Axios stent. It is also made of nitinol wire, fully covered, delivered with a 10Fr system, and has large diameter flanges that transmit even pressure on the lumen wall. The diameter of the flanges at both ends is 25 mm (Fig 2). One unique feature of the Spaxus stent is that the flanges fold back once fully deployed which is proposed to enhance lumen apposition and prevent migration. The available diameters of the stent are 8 mm, 10 mm, and 16 mm, and the length is 20 mm, but the distance between the flanges is 5 mm after folding back with deployment.

2. Indications for LAS

1) Pancreatic fluid collections (PFCs)

i) There have been multiple studies to date examining the safety and efficacy of LAMS (the majority of available prospective data pertains to the Axios stent) when used to drain pancreatic fluid collections (PFCs). Itoi et al., first reported use of Axios stent for symptomatic pancreatic pseudocysts in 2012 (15 patients). All stents were successfully deployed without complication (median time of removal 15 days) with only one stent migration reported. All patients had complete resolution of their collections following initial procedure and no recurrence during the year of follow-up. In addition, they demonstrated the safety and feasibility of performing pancreatic necrosectomy through the deployed Axios stent.

ii) Gornals et al. next published a study in 2013 comparing Axios (n = 9) with plastic double pigtail stents (n = 10). The technical success rate for Axios was 88.8% with one reported delivery system failure. All patients achieved complete PFC resolution following the initial procedure (stent retrieval 33 ± 40 days). However, there was one pseudocyst recurrence one month after stent removal and one pneumothorax was seen after trans-esophageal drainage. When compared to plastic pigtail stents, the Axios stent showed similar technical and clinical success. However, the patients with double pigtail stents higher rates of complications, recurrences, and stent migrations.

iii) This year Shah et al. published a prospective, multicenter study in 33 patients that showed that Axios
were placed successfully in 91% of subjects with pancreatic fluid collections with a 93% resolution rate.\(^7\) Complications (15%) included abdominal pain (n = 3), spontaneous stent migration, back pain (n = 1), access-site infection, and stent dislodgement (n = 1).

2) EUS-guided Gallbladder drainage (EUS-GBD)

i) EUS-GBD is a relatively new approach with limited published data. One retrospective study in 15 non-surgical candidates who underwent EUS-GBD with LAMS to decompress the gallbladder (7 patients calculous cholecystitis, 4 acalculous cholecystitis, 2 patients biliary obstruction, 1 patient gallbladder hydrops, 1 patient symptomatic cholelithiasis).\(^8\) All had refused percutaneous drainage. Technical success was reported as 93% with only one patient developing post-procedure fever. However, major study limitations are its small sample size and retrospective design.

ii) A larger, multicenter prospective trial examined the safety of LAMS for EUS-GBD in 30 patients.\(^9\) Technical success was achieved in 90% and clinical success rate was 96%. LAMS removal was performed in 15 of 30 patients (50%) after a mean of 91 days (SD±24 days). In 15 patients (50%), no LAMS removal was performed because of death (n=5), significant tissue overgrowth (n=2) or other causes (n=8). The authors reported a high rate (50%) of serious adverse events (SAEs) in 15 patients that included stent occlusion with recurrent cholecystitis.

iii) Prior studies on EUS-GBD utilized standard LAMS, but there has been a report of utilizing the modified HotAxios stent with the cautery capability on the tip to aid with passage of the delivery system through the GI tract lumen and into the gallbladder without the need for tract dilation prior to stent deployment.\(^10\)

3) EUS-guided Gastrojejunostomy

i) Itoi et al. was the first to describe the technique of using LAMS for EUS-guided gastrojejunostomy in 2013.\(^11\) Itoi’s group has lead the research on this technique and has published further results more recently. This technique involves utilizing a specially created double balloon enteric tube (Tokyo Medical University type, Create Medic, Yokohama, Japan) to help stabilize the small bowel adjacent to the stomach in the area of puncture and LAMS placement.

ii) Itoi et al. conducted an animal study examining the use of different types of LAMS (Axios, HotAxios, and Spaxus) for creation of gastrojejunostomy.\(^12\) Survival experiments were conducted for one month and showed animals had normal eating behavior and no signs of infection. On follow-up endoscopy, the LAMS appeared patent and once removed a mature stoma was noted which allowed for easy scope passage from the stomach into jejunum.

iii) Finally, Itoi and colleagues have just published their results in the first prospective study on EUS-guided double balloon occluded gastrojejunostomy bypass (EPASS) using a LAMS in 20 patients.\(^13\) Technical success rate was 90% but in the 2 failed cases there was misdeployment of the distal flange resulting in pneumoperitoneum and perforation.

4) EUS endoscopic ultrasound-directed transgastric ERCP for patients following roux-en-Y gastric bypass (RYGB)

Due to the exclusion of the distal stomach and proximal duodenum in RYGB, the ampulla cannot be accessed in a standard fashion for ERCP. Although deep enteroscopy can be performed, there are variable rates of
success. Recently, use of LAMS to provide access to the excluded GI tract lumen for passage of the duodenoscope for ERCP has been proposed. The ability to perform ERCP during the index procedure was successful in 3 of 5 cases (60%). Two LAMS dislodgments requiring restenting were observed. No major adverse events were observed. Major limitation is the extremely small sample size of only 5 patients and larger studies are needed to further assess safety, efficacy and long term follow-up including durability of fistula closure and any effects on weight gain.

II. Therapy

1. EUS Radiofrequency Ablation (RFA) Probe

The HabibTM EUS RFA probe (Fig. 3) is a novel monopolar catheter that can be used to cauterize and coagulate tissue. This probe consists of a 1 Fr wire (0.33 mm, 0.013”), which has a working length of 220 cm and can be passed through a standard 19 or 22-gauge EUS needle. Radiofrequency power is applied to the 20 mm electrode at the end of the wire to cauterize or coagulate tissue. The HabibTM EUS RFA is CE marked for use in Europe and FDA approved for use in U.S.A. EUS-guided RFA has been described as a potential treatment for pancreatic cystic neoplasms and neuroendocrine tumors. This prospective study examined the use of EUS-guided RFA in 8 patients with pancreatic lesions (6 cystic neoplasms, 2 neuroendocrine tumors). All lesions were successfully ablated and in 6 month follow-up: 2 cysts resolved, 3 cysts had 50% reduction in size, and 2 neuroendocrine tumors developed central necrosis. No serious complications were observed. Further large-scale studies are warranted to assess the safety (particularly, rates of pancreatitis) and efficacy of this novel treatment modality.

2. Preloaded Fiducial Needle

In recent years, multiple studies have demonstrated the feasibility and safety of fiducial marker placement under EUS guidance (with or without fluoroscopic assistance) to facilitate radiation therapy in pancreatic cancer. Disadvantages of the typical back-loading technique used include being time consuming to individually load small markers into the tip of a 19 or 22-gauge EUS needle by hand and variable deployment via passage of stylet or saline through needle. Typically 3-4 markers are needed and therefore the needle has to be removed and reloaded for each marker. Recently, new EUS needles have been developed that have multiple fiducial markers already preloaded to save time and allow for more accurate deployment with tactile feedback. Currently, the only FDA approved fiducial needle in the U.S.A. is the Echotip fiducial needle by Cook Medical (Bloomington, IN, USA) (Fig. 4).
4). This is a 22-gauge needle that contains 4 gold fiducial markers. Another preloaded fiducial needle model is currently being developed by Medtronic (Sunnyvale, CA, USA) in both 19 and 22-gauge needles and comes preloaded with 2 fiducial markers.

III. Advanced imaging: Needle based confocal endomicroscopy

Confocal laser endomicroscopy (CLE) is an endoscopic technique developed to obtain images that are high resolution and magnification. The ASGE recently published a review of this innovative technology.\textsuperscript{18} CLE is based on tissue illumination with a low-power laser with subsequent detection of the fluorescence of light reflected from the tissue through a pinhole (Fig. 5). The term confocal refers to the fact that both illumination and detector systems are in the same focal plane. Light is focused at a selected depth in the tissue of interest and reflected light is then refocused onto the detection system by the same lens. Only returning light refocused through the pinhole is detected and light scattered at other angles are excluded from detection. This allows CLE to obtain real-time cellular imaging and evaluation of tissue architecture during endoscopy through the use of topical and/or intravenous fluorescence contrast agents to generates images with resolution similar to traditional histological examination.

The probe-based CLE (pCLE) system is comprised a low powered laser with an integrated distal lens. The probe-based system (Cellvizio confocal probes, Mauna Kea Technologies, Paris, France) can create cross-sectional images at different depths and the probe’s individual optical fibers function as the pinhole. Needle based confocal endomicroscopy (nCLE) utilizes the AQ-Flex 19 probe through a 19-gauge EUS needle (Fig. 6a and 6b). The depth of imaging is 40 to 70 mm, the maximal field of view is 325 mm, and resolution is 3.5 mm.

A. Our center reported results from the initial feasibility trial studying the nCLE probe in pancreatic lesions in 2011.\textsuperscript{19} We demonstrated technical succes in 17/18 patients, had 2 cases of pancreatitis, established imaging criteria, and created a standardized protocol for use.

B. Then these results were validated in a prospective, multicenter study that included 65 patients.\textsuperscript{20} The major finding of this study identified that papillary (finger-like) projections had a 100% specificity for intraductal papillary mucinous neoplasms (IPMN). However, the study also showed that there were limitations due to variations in the location of probe within a cyst and the epithelium of IPMNs themselves that lead to a
low sensitivity of only 59%.

C. Most recently in 2015, Napoleon et al. identified a new imaging criterion for diagnosing serous cystadenomas: superficial vascular network (SVN). Although nCLE again had a low sensitivity of 69%, if the SVN was visualized then it was 100% specific for serous cystadenomas with a 100% positive predictive value.

IV. New scopes: Forward viewing linear echoendoscope

The main limitation of the standard curvilinear array EUS (CLA-EUS) scope is that any device that exits the accessory channel is oblique to the endoscope axis making passage of accessories difficult. The standard CLA-EUS scope has an oblique view of 100° and an endoscopic view that is 55° rotated with respect to the axis of the endoscope and the ultrasound probe. Recently, a forward-viewing linear echoendoscope (FV-EUS, Olympus America, Center Valley, PA, USA) has been developed that shifts the orientation of both the endoscopic and ultrasound views from oblique to forward.

A. Earlier this year, Fucci et al. published an article illustrating the device specifications of the FV-EUS scope as shown below. The FV-EUS ultrasound transducer is located adjacent to the working channel, at the tip of the endoscope, in order to display a forward-viewing image (Fig. 7a). This change now permits devices to come out parallel to the longitudinal axis of the endoscope, which could have the potential to allow for easier passage of devices and stents compared to standard CLA-EUS by allowing for better visualization and increased application of mechanical force. However, the ultrasound scanning area is now limited to only 90° (compared to 180° in standard CLA-EUS scopes) and the 3.7mm working channel lacks an elevator, which may represent design limitations (Fig. 7b).

![Fig. 7a and 7b. Showing tip of the FV-EUS scope and range of view. Fuccio et al, J Hepatobil Panc Sci. 2015](image)

B. The FV-EUS scope has two potential advantages over standard CLA-EUS scopes: (1) elimination of need to change endoscopes when a forward-viewing endoscope is necessary for endoscopic visualization; and (2) ability to reach or inspect areas of the gastrointestinal lumen not easily accessible with the CLA-EUS. However, data to date has not shown a significant clinical benefit. One multicenter, prospective European study included 58 patients with PFCs that were randomized to drainage with either standard CLA-EUS vs FV-EUS, but their results did not show a difference in ease of drainage, safety, or efficacy between the two scope types.

C. In our own center, we have used the FV-EUS to pass deeply into the afferent limb in a patient who
underwent Whipple resection and then developed a post-operative abscess in the surgical bed (Fig. 8A). The abscess was adjacent to the afferent limb at approximately 60cm distal to the gastrojejunal anastomosis. The added benefit of enhanced forward viewing endoscopic ability allowed us to pass the scope down the afferent limb and identify the collection. However, due to lack of an elevator we could not obtain a satisfactory angle for puncture, therefore switched back to standard CLA-EUS for guidewire puncture and stent placement (Fig. 8B).24

![Fig. 8. (A) FV-EUS view of collection (note the limited sonographic range). (B) Standard CLA-EUS view of collection with needle angled down towards collection using the elevator.](image)

**Conclusion**

Recent technological advances have made EUS a safe and effective method of providing a broad range of treatments and therapies previously not thought possible. The development of new stents for various procedures has expanded the ability to effectively collect fluids from the pancreas and gall bladder, perform gastrojejunostomy, and facilitate ERCP in gastric bypass patients. Additional tools allow novel therapies for treatment of pancreatic tumors, such as radiofrequency ablation and fiducial markers to guide radiation therapy. Furthermore, advanced imaging modalities such as needle-based confocal laser endomicroscopy (nCLE) have allowed us to visualize the inside of pancreatic cystic lesions and help in making a diagnosis. Finally, the development of new echoendoscopes, such as the forward-viewing linear echoendoscope (FV-EUS), has the potential to allow better visualization of the GI tract and potentially have added efficiency for therapeutic maneuvers. Through these additions to the endosonographer’s arsenal of tools, EUS continues its transition from a diagnostic modality to a more therapeutic procedure. As innovation in the field continues, we hope to see additional tools expanding the use of EUS well beyond its current limits with the ultimate goal of improving patient outcomes.

**References**