The first natural orifice transluminal endoscopic surgery (NOTES) in a swine model was reported at Digestive Disease Week (DDW) in 2000, and it has now been one decade since the first human case video demonstration. Ten years later, the field is evolving and maturing. A range of procedures such as single-port surgery, hybrid surgery, endoscopic submucosal dissection (ESD), and per-oral endoscopic myotomy (POEM), are now often grouped under the NOTES umbrella though they may not use a natural orifice, and they may not be transluminal. POEM is considered by some to be the first sentinel application in NOTES. Hybrid and submucosal approaches to upper gastrointestinal tumors in humans may spare major organ resection with life-long quality-of-life implications. At DDW 2012 (19-22 May, San Diego, California, USA) data were presented on pure NOTES procedures performed using only conscious sedation, and percutaneous flexible endoscopy-based extraction of gallstones was demonstrated. Although growth in the field is escaping strict definitions, the concept of NOTES continues to embolden progress on a host of clinical problems. At DDW 2012, there were 22 NOTES abstracts and 4 POEM abstracts, representing a steady level of research, following 26 abstracts in 2010 and 25 in 2011. The top 20 abstracts of 2012 are reviewed below.

HYBRID NOTES

Hybrid approaches generally refer to procedures performed using transcutaneous rigid laparoscopes combined with flexible endoscopes passed via a natural orifice. A study of 22 human patients described NOTES endoscopic full-thickness resection of early gastric cancer combined with laparoscopic regional lymph node dissection. En bloc resection with negative surgical margins was achieved in all cases. No recurrence or metastasis was noted during a median follow-up period of 566 days. This study is remarkable in providing a less morbid approach than total gastrectomy while addressing the components of a traditional cancer operation.

The same authors also reported on the comparison between laparoscopic wedge resection and hybrid NOTES for intraluminal subepithelial tumors in 29 patients. In a hybrid approach, full-thickness incision of the gastric wall was carried out endoscopically and the closure was performed laparoscopically. A total of 17 patients underwent laparoscopic wedge resection and 12 patients underwent hybrid NOTES. The hybrid NOTES approach appeared to enable a smaller, more targeted resection than the wedge approach.

In the third abstract from the same group, the authors looked at the combination of sentinel node surgery and hybrid NOTES in early gastric cancer. Indocyanine green was used to map sentinel nodes. If sentinel nodes were positive for metastasis, gastrectomy and lymph node dissection were performed. If the nodes were negative, ESD was used for local resection of the early gastric cancer. The procedure was technically feasible and was suggested as a bridge between EMR, ESD, and laparoscopic surgery.

A prospective, quality-of-life study compared a laparoscopic appendectomy to a hybrid NOTES transvaginal appendectomy in 20 female patients (10 in each arm). Although the average procedure duration was shorter with the laparoscopic approach, patients in the hybrid NOTES arm appeared to have a better postoperative course in the early period, with better activity (Day 1-14), postoperative pain (Day 1), and quality of life (Day 3). The only significant complication was an intra-abdominal abscess in the laparoscopic group. Though small, the study is noteworthy in undertaking a prospective comparison between a NOTES approach and a standard approach.

COMPLICATIONS IN NOTES

A randomized study looked at the hemodynamic changes during transesophageal NOTES and conventional mediastinoscopy in 20 swine. Three animals in the NOTES group developed a tension pneumothorax, which...
required percutaneous decompression with no further repercussions. Both procedures were tolerated well with no significant difference between hemodynamic and respiratory parameters.

Inflammatory response to transgastric and transcolonic NOTES and to laparoscopic peritoneoscopy was compared in a study of 30 pigs. Changes in systemic inflammatory markers such as C-reactive protein, tumor necrosis factor-α, interleukin-1β, and interleukin-6 were similar in all three groups. At necropsy, major adhesions between the bowel loops were seen in two animals in the colonic group. In a third of the animals in the NOTES group, microscopic signs of mucosal inflammation of uncertain significance were observed at the site of closure. Overall, transcolonic, transgastric, and laparoscopic procedures resulted in similar changes in inflammatory markers.

A retrospective analysis compared immediate postoperative pain in patients who underwent transvaginal cholecystectomy (TVC) and laparoscopic cholecystectomy. Postoperative opioid use was compared in 20 patients in each group. Although there was no difference in the visual analog pain scale, patients in the TVC group used significantly less opioid in the postanesthesia care unit than patients in the laparoscopic cholecystectomy group. This study is also significant in beginning to provide some comparative data regarding the NOTES and laparoscopic approaches.

A large retrospective study presented data on gynecological and fertility issues in 107 patients who underwent NOTES procedures using transvaginal access. Gyne-
ocological assessment including history, and physical and colposcopic examinations were performed at postoperative Days 7, 30, 60, 180, and 360. Adequate healing of the vaginal access without any local complications was observed in all patients. One of the patients suffered from dyspareunia. A total of 13 patients became pregnant after the procedure, 10 resulting in a normal vaginal delivery and 3 in Cesarean section. The transvaginal route has emerged as the most common approach, assessment of outcomes following transvaginal access is of considerable importance.

NEW TECHNIQUES

The utility and safety of a computed tomography (CT)-based image registered navigation system to identify mediastinal structures was studied in a NOTES mediastinoscopy porcine model. A total of 13 pigs underwent image registered-guided safe access (IR-MED) and 15 procedures used a blind access (MED). Mediastinoscopy was not possible in two animals in the MED group but was possible in all animals in the IR-MED group. The mean number of identified organs was slightly higher in the IR-MED group. Image registration provides potential benefit in NOTES procedures above and below the diaphragm.

Another study evaluated the diagnostic and therapeutic potential of NOTES using a forward-viewing echoendoscope. Transgastric peritoneoscopy with a forward-viewing echoendoscope was performed in 10 animals. Endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) of the liver, spleen, and kidney was performed successfully in nine out of 10 animals using a 19-G needle. EUS-guided radiofrequency ablation (RFA) of the hepatic parenchyma was performed successfully in six animals. Argon plasma coagulation was used to control minor bleeding after endoscopic biopsy from the liver and spleen in four animals.

A pig model was used to evaluate the use of a small-caliber endoscope for the extraluminal observation of a gastric full-thickness resection. The small-caliber endoscope (3.2 mm) was introduced into the peritoneal cavity through the gastric wall. Three of the eight full-thickness resections had branches of the gastroepiploic artery in the field of resection and one of six NOTES incisions had a blood vessel in the plane of resection. The presence of the observation endoscope was felt to improve confidence and might help safeguard against hemorrhage.

A water jet-assisted Hybrid Knife (ERBE, Tübingen, Germany) was compared with a conventional electric knife for endoscopic resection of upper gastrointestinal submucosal tumors. In this randomized controlled trial, 16 patients underwent submucosal tunneling endoscopic resection (STER) with the Hybrid Knife (Group A) and 15 patients underwent STER with the conventional electric knife (Group B). The average procedure duration (50.5 vs. 78.7 minutes) as well as hemostatic applications for intra-operative bleeding in Group A were significantly less than that in Group B. No evidence of recurrence was seen after 3-9 months of follow-up. This study is important because it highlights device development specific for NOTES-type applications. The combination of water jet and electrocautery decreased exchanges and the need for hemostasis and is an example of NOTES-specific technologies that improve procedural efficiency and outcomes.

TRAINING

A model for simulated NOTES sigmoidectomy was developed and its impact on the training of endoscopists was studied. Two colorectal surgeons and two interventional endoscopists underwent training for NOTES sigmoidectomy using a hybrid simulator model. A standardized technique was designed and each participant underwent four mentored training sessions. An unmentored final test was carried out with predetermined proficiency criteria. Training resulted in a 42% decrease in the operating time. No complications occurred during the final test procedures. Training in NOTES represents a major unknown, with skill
sets often residing across specialties and no guidelines or clear pathways to proficiency.

The German NOTES registry was used to study the learning curve for TVC. Data were available for 1823 TVCs. Procedure duration was significantly shorter at high-volume centers (>100 procedures) than at low-volume centers (<100). The complication rate did not differ between the groups. The authors concluded that the learning curve for the procedure duration with TVC reaches a plateau after 50 procedures. TVC was however deemed safe even in low-volume centers when performed by experienced surgeons.

**PER-ORAL ENDOSCOPIC MYOTOMY**

A retrospective review presented data on 205 patients with esophageal achalasia who underwent POEM. The procedure was successful in 202 patients (98.5%). It failed in three patients due to submucosal fibrosis from previous therapies. The mean procedure duration was 68.5 minutes. The average length of the endoscopic myotomy of the inner circular muscle was 9.5 cm. During the mean follow-up period of 8.5 months, dysphagia was relieved in 199 patients post-POEM and no serious complications were observed.

A group from the United States presented data on POEM performed in 12 patients with esophageal achalasia at a single center by a gastroenterologist. POEM was successful in 11 out of the 12 patients with significant decrease in Eckardt score and mean esophageal sphincter (LES) pressure. One patient underwent pneumatic dilation as symptoms did not improve after POEM. Mean POEM procedure duration was 150 minutes and the average length of myotomy was 5.5 cm. None of the patients suffered from significant gastroesophageal reflux after POEM.

A prospective, multicenter, international study presented results of a POEM trial consisting of 51 patients with primary achalasia. Treatment success (Eckardt score <3) was seen in 94% patients. Mean LES pressure was significantly lower after the procedure. Esophageal perforation occurred at the mucosal entry site in one case. One patient had an esophageal ulceration and another had an ulceration in the cardia. The complications resolved without sequelae.

A randomized study compared water jet-assisted Hybrid Knife POEM with conventional POEM in 43 patients. The primary endpoint was duration of procedure. POEM performed with a water jet-assisted Hybrid Knife was of significantly shorter duration (21.8 vs. 36.9 minutes; P < 0.0001). The length of the mucosal incision as well as the length of the circular muscle incision was comparable between the two groups. The water jet-assisted group had a significantly lower bleeding rate and less frequent usage of the coagulation forceps for the treatment of intraoperative bleeding. POEM is emerging as a remarkably successful procedure, with measurable manometric improvements and clinical resolution of dysphagia in the majority of patients.

**CLOSURE**

One study presented the results of use of a bioabsorbable polymer (BAP) for operative closure following NOTES procedures in the stomach, and small and large intestine in a pig model. During the 10-week follow-up period, the pigs did not exhibit a loss of appetite and survived until sacrifice. No adherence to the surrounding organs or infection was observed. The BAP was completely absorbed and histology did not show remaining polymer.

Comparison of a continuous suture line vs. interrupted stitches created by a novel endoscopic suturing device was evaluated in a randomized animal trial. In 16 animals, transgastric access was achieved utilizing a gastric wall puncture and 20-mm controlled radial expansion balloon dilation. Suturing of the gastric wall incision was felt to be easily achieved and was airtight in all animals. The mean time to complete a continuous suture line was 7.43 minutes vs. 10.49 minutes with interrupted stitches. Post-mortem examination revealed no signs of peritonitis or other intraperitoneal complications. Closure remains a major issue in NOTES, and is often more of a challenge than the primary procedural intervention.

**DISCUSSION**

NOTES research has been at a stable level over the past 3 years at DDW with 26 abstracts falling loosely within the NOTES spectrum in 2012. Novel procedures continue to be developed and reported, and refinements may allow for all aspects of a traditional surgical approach to be recapitulated in a minimally invasive manner.

Hybrid NOTES combines laparoscopic and endoscopic technologies and is commonly used because it can solve problem areas in NOTES such as closure. The hybrid approach has been used for cholecystectomy, appendectomy, sleeve gastrectomy, sigmoidectomy, liver biopsy, and splenectomy, and more recently for management of foregut mass lesions. Although hybrid procedures are not completely scarless, they may facilitate novel minimally invasive techniques and provide a critical safety component for new approaches. Using endoscopy and laparoscopy, it may be possible to perform a complete recapitulation of more traditional major open surgeries as demonstrated this year at DDW. In a recent review of NOTES procedures in humans, 54% were hybrid techniques, highlighting the penetration and importance of the approach.

Heller myotomy is a popular treatment for achalasia owing to its effectiveness and the ability to use a laparoscopic approach. However, it may result in significant...
gastroesophageal reflux requiring additional antireflux surgery. POEM is a minimally invasive technique for the treatment of achalasia. Its advantages over a traditional laparoscopic myotomy include a scarless technique and the capability of performing a very long myotomy of the thoracic esophagus. The possibility of vagal nerve injury, with the risk of delayed gastric emptying could be reduced. It is rapidly becoming a benchmark NOTES-type procedure, with larger human studies being reported in Asia, Europe, and North America. Data to date suggest a high degree of safety, excellent clinical outcomes, reproducibility in multiple centers, and concurrent quantifiable improvements in manometric parameters. POEM is seen by some as the first sentinel application in NOTES.

Technology development in NOTES continues. Forward-viewing echoendoscopes represent development in the EUS platform and this year were reported in combination with a NOTES approach. The use of the water jet-assisted electrocautery equipment (Hybrid Knife) demonstrates the benefit of development for specific NOTES applications. Image registration systems are already in use in areas such as otolaryngology and interventional pulmonology and a CT-based image registered navigation system with a NOTES approach was reported this year providing the positional information on the endoscope within and around a cavity. It is hoped that industry will continue to invest in and develop technology specific to NOTES.

A major shortcoming has been the lack of comparative data evaluating NOTES vs. traditional or standard approaches. In a small human study, patients who underwent a transvaginal NOTES appendectomy had better early activity, less initial pain, and better early quality of life than those who underwent a laparoscopic appendectomy. Albeit in an animal model, Hucl et al. demonstrated that NOTES peritoneoscopy is comparable to laparoscopy in terms of markers of inflammation post-procedure. In a retrospective analysis, patients undergoing transvaginal cholecystectomy used less opioids in the postanesthesia care unit than did patients undergoing laparoscopic cholecystectomy. The field is still in need of large prospective human trials comparing NOTES with standard approaches.

DDW 2012 marks the 10-year anniversary of the first report of a human NOTES procedure. Over the past 3 years, interest and research in NOTES has been stable with similar numbers of abstracts appearing at DDW in 2010, 2011, and 2012. An expanding set of endoscopic surgical procedures such as mucosal resection, ESD, and POEM are at times grouped under the NOTES umbrella, though they may differ in fundamental ways. POEM probably represents the first sentinel application in NOTES and has the potential to supplant a current standard. Rather than recapitulating safe and efficacious laparoscopic surgeries, NOTES may also offer unique and differentiated capabilities. Along with procedures such as POEM, hybrid management of foregut mass lesions and ESD combined with laparoscopic lymph node dissection appear to offer substantial compelling benefits beyond the standard approach. Reliable closure of the viscerotomy has remained a challenge in NOTES for more than a decade, and there is still no established technological solution. There is progress this year with abstracts comparing NOTES and standard approaches, but the field is still in need of large prospective comparative trial data for NOTES vs. laparoscopic and/or open surgery. NOTES continues to present an appealing prospect of scarless surgery, with no wound infections or hernias and less postoperative pain. The field has inspired downstream innovation and novel NOTES approaches are delivering substantial benefits over traditional approaches in case series. Continued investment and innovation in NOTES seems likely to deliver on the initial promise of improved minimally invasive approaches to common clinical presentations.

REFERENCES


