Original Paper

Feasibility Study of EUS-NOTES as a Novel Approach for Pancreatic Cancer Staging and Therapy: An International Collaborative Study

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Key Words:
NOTES; EUS; Pancreatic cancer; Diagnosis; Staging; Pancreatic carcinoma; Endosonography.

Abbreviations:
Natural Orifice Translumenal Endoscopic Surgery (NOTES); Endoscopic Ultrasound (EUS); Endoscopic Ultrasound Fine Needle Aspiration (EUS-FNA); Laparoscopy (LAP); Laparoscopic Ultrasound (LUS); Ultrasound (US); Computed Tomography (CT); Magnetic Resonance Imaging (MRI); Positron Emission Tomography - Computed Tomography (PET-CT).

ABSTRACT

Background/Aims: EUS guided Natural Orifice Transluminal Endoscopic Surgery (NOTES) could be a potentially viable approach for pancreatic surgery. EUS-guided access through the stomach wall may prove to be a safe and effective method for accessing the pancreas. The aim of the study was to assess the EUS-guided diagnostic and therapeutic procedures during NOTES for both anterior and posterior approach of the pancreas. **Methodology:** The feasibility of peritoneoscopy through an anterior EUS-guided transgastric approach, as well as direct access to the pancreas through a posterior EUS-guided transgastric approach was tested for ease of access to the tail of the pancreas. Gastric wound closure was finally performed in several animals using various commercial and prototype endoscopic accessories. **Results**: The results showed the ability of EUS-NOTES technology to facilitate a transgastric approach and provide both an anterior and posterior access the pancreas. Identification the pancreatic tail by EUS with the aid of EUS-guided T-tag insertion, as well as posterior access and subsequent inspection/dissection of the pancreatic tail may also be possible. **Conclusions:** It is technically possible by EUS-guided NOTES procedures to achieve a systematic anterior and posterior access for NOTES transgastric peritoneoscopy and direct pancreatic endoscopic procedures.

INTRODUCTION

Pancreatic cancer has a dismal prognosis due to its late diagnosis, low resectability rate and poor survival outcome after curative surgical resection (1). Surgical resection (2) represents the only chance for cure, but only 10 to 20% of patients have an early diagnosis and only 25% of patients benefit from such a radical procedure (3,4). Even after curative surgery the 5-year survival rate in this group is only 25%, with most of the patients developing distant recurrence within 2 years. The principle hurdle for tumor resectability is tumor involvement of major arterial and venous vascular structures adjacent to the pancreas (5). Spiral CT imaging is considered the standard for initial diagnosis, staging and resectability (6). Endoscopic ultrasound (EUS) is also considered an important method to confirm the diagnosis principally due to the ability to obtain EUS-guided fine needle aspiration (EUS-FNA) biopsy to confirm the diagnosis (7). However, small superficial hepatic and peritoneal metastases tumors are often below the limit of detection of both CT and EUS which results in false negative studies.

Diagnostic laparoscopy (LAP) can identify peritoneal carcinomatosis or superficial liver metastases often missed by routine imaging tests (8), and laparoscopic ultrasonography (LUS) can further enhance its capabilities (2,4). When compared to laparotomy in cancer patients, laparoscopy possesses many described advantages including: less immune depression, faster healing, fewer parietal complications, faster recovery, decrease of hospitalization and reduced costs (8).

The emerging method of Natural Orifice Transluminal Endoscopic Surgery (NOTES) could offer a theoretical advantage over laparoscopy in pancreatic cancer patients (9). Anatomically, the stomach is positioned immediately anterior to the pancreas and provides access to both the lesser and greater omental bursa. Additionally, the stomach possesses a robust arterial blood supply and excellent healing properties (10). Therefore access through the posterior stomach may provide safe and efficient access to the pancreas and lesser omental bursa (11) while an anterior transgastric approach could allow for staging of the larger peritoneal cavity and liver (12,13).

The aim of this study was to use EUS-guided and

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NOTES techniques to test the feasibility of an anterior and posterior transgastric approach for use in pancreatic cancer staging.

METHODOLOGY

The study was performed on a swine model due to its similarity to human anatomy and ability to accommodate adult size endoscopic instruments. We used eight live animals in this pilot/feasibility study after approval by the Institutional Animal Care and Use Committee of MD Anderson Cancer Center.

Live animal study

Eight live Yorkshire cross pigs underwent general anesthesia for upper gastrointestinal endoscopy and EUS. Initial sedation was performed with ketamine (22-33mg/kg) and aceparomazine (0.22-1.1mg/kg) IM. Anesthesia was maintained with isofluorane 1-3% inhalant. We subsequently tested the feasibility of peritoneoscopy through an anterior EUS-guided transgastric approach, as well as direct access to the pancreas through a posterior EUS-guided transgastric approach. After the procedures gastric wound closure was finally performed in all animals using various commercial and prototype endoscopic accessories that can potentially achieve this goal, including T-tags (Wilson-Cook, Winston Salem, New York) and OTSC clips (Ovesco Endoscopy AG, Tuebingen, Germany).

Continuous video recordings of the procedures were obtained. Specifically, the following parameters were measured: complete time of procedure from sedation until gastrostomy closure, traumatic injuries during the procedure and intraoperative mortality before euthanasia.

Anterior approach (3 pigs)

After EUS inspection of the anterior gastric wall and surrounding structures, an area devoid of any major vessels was chosen for puncture. Puncture of the gastric wall was achieved using a 19G needle with stylete under EUS-guidance (**Figure 1A**). The needle stylet was retracted and exchanged with a 0.035 hydrophilic guidewire which was coiled inside the peritoneum. Needle-knife incision followed by balloon dilation over the guidewire provided transgastric access to the peritoneal cavity (**Figure 1B,C**). The anterior access created to the peritoneal cavity allowed passage of a single channel endoscope, as well as of the linear EUS scope. Pneumoperitoneum was established by air insufflated from the endoscope.

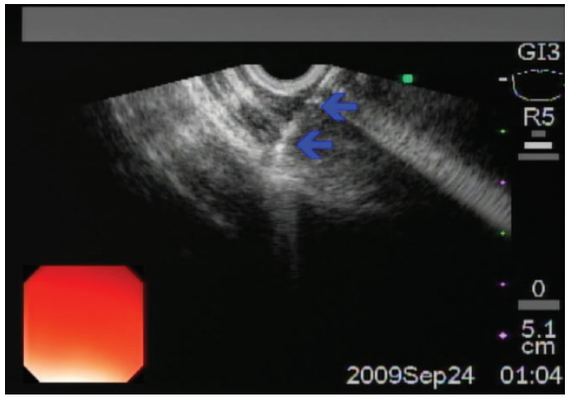
A long spinal type needle was inserted percutaneously into the anterior abdominal wall to avoid increase of intraperitoneal pressure through over inflation. Peritoneoscopy was then performed with a normal diagnostic gastroscope which allowed inspection of the abdominal viscera and peritoneum with biopsy (**Figure 1D**).

Posterior approach (5 pigs)

After EUS inspection of the posterior gastric wall, pancreatic body and tail, and surrounding structures (left adrenal, left kidney, splenic artery and vein, etc.), an area devoid of any major vessels was chosen for puncture, at the level of the pancreatic body. The tail of the pancreas was localized by EUS-guided tattooing (GI spot ink, US supply, USA) or EUS-guided insertion of T-tags (prototype Cook, USA) for later identification and verification (**Figure 2A**). Puncture of the gastric wall through the serosa was achieved using 19G needle with stylet under EUS-guidance. The stylet was retracted and 100mL saline was injected posterior to the stomach in the lesser omental bursa in order to create a bleb for secure access (**Figure 2B**). A 0.035 hydrophilic guidewire was coiled inside the space created by saline injection, likewise guided by EUS. Access was provided through the stomach by EUS-guided needle-knife incision, followed by balloon dilation over the guidewire. The posterior access thus created allowed further passage of a conventional forward viewing endoscope. The pancreas was identified by intermittent traction on the T-tag thread, with subsequent dissection and exposure of the body/tail region with a needle knife (**Figure 2C**). The pancreatic tail parenchyma was verified either by con¬ven¬tional endoscopic biopsies (**Figure 2D**) or by transabdominal exploration with verification of the ink tattoo. Closure of the gastrostomy was achieved as previously described, by using Triclips, T-tags or OTSC clips.

Pathological examination

All the animals survived the acute procedures prior to euthanasia. To examine the effectiveness of the gastric closure, the stomach and adjoining esophagus and duodenum were removed after euthanasia in representative animals from each study group. Dye was injected intralumenally into the gastric cavity and after both the esophagus and duodenum was occluded. The specimen was then placed in a water-bath to check for water-tight seal at the gastrostomy site. For the cases where direct pancreatic biopsies were performed, the presence of pancreatic tissue within the biopsy specimen was verified by microscopy.



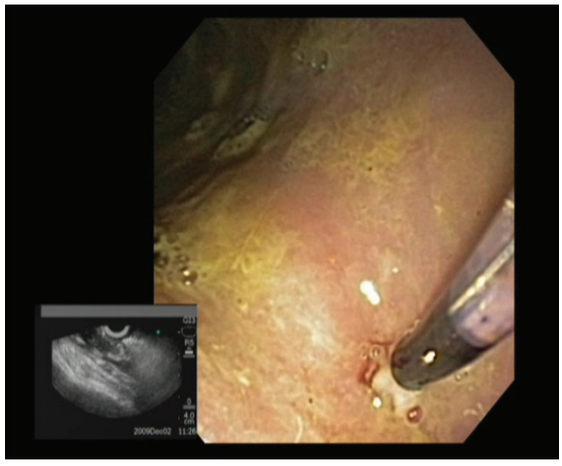


FIGURE 1. (A) EUS-guided puncture of the anterior gastric wall (arrows); (B) EUS-guided needle knife incision of the anterior gastric wall; (C) Baloon dilatation over the guidewire of the anterior gastric wall; (D) Peritoneoscopy performed after transoral, transgastric access.

RESULTS

A total number of eight pigs were used for this initial pilot study, three were used for the transgastric anterior approach and five for the posterior transgastric approach. Details of the procedures are included in Table 1. Initial access was performed through direct incision in one pig after creating a submucosal bleb and with EUS-guidance in the other seven pigs. The only animal injury was recorded during the first animal procedure when a burn injury to the peritoneum and anterior abdominal wall occurred during transgastric access.

Procedures performed after transgastric access included peritoneoscopy of the greater and lesser omental bursa and direct pancreatic vizualisation. Subsequent inspection and exploration of the pancreatic tail with direct endoscopic biopsies was successfully performed in five pigs. The gastrostomy orifice was closed with a modified T-tag prototype (Wilson-Cook, Winston-Salem, NY) in two pigs, Triclips (Wilson-Cook, Winston-Salem, NY, USA) in one and with over-the-scope clips (OVESCO Endoscopy AG, Tuebingen, Germany) in one (Figure 3A). In the first animal in which Triclips were used for closure, leak test was not done as the closure was not successful as apparent on endoscopic inspection during the procedure.

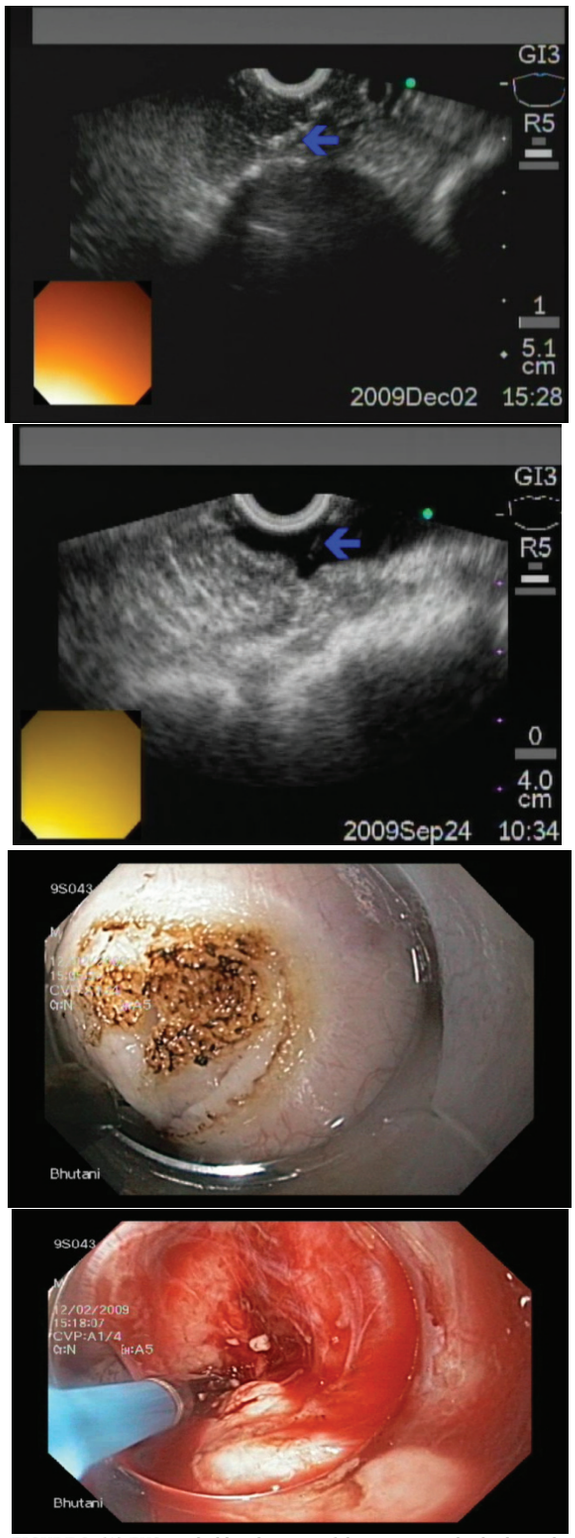


FIGURE 2. (A) EUS-guided localization of the pancreatic body through insertion of a prototype T-tag (arrow); (B) EUS-guided injection (arrow) of 100mL saline between the gastric wall and pancreatic body, in order to provide a bleb for safe posterior transgastric access; (C) Dissection and exposure of the pancreatic body / tail after EUS-guided posterior access through a transoral, transgastric route; (D) Direct endoscopic biopsies of the pancreatic tail, after EUS-guided posterior access through a transoral, transgastric route.

DISCUSSION

Reliable staging and assessment of resectability play an important role when planning surgical intervention for pancreatic cancer (14). Ultrasonography is also sometimes used during open surgery such as in liver surgery, where it is employed to evaluate the vascular anatomy and the relationship of the tumor with the main Glissonian pedicles and suprahepatic veins (15). It plays an more important role in laparoscopic surgery in order to detect and localize small liver metastasis (15), small pancreatic tumors (2) or to explore the extrahepatic biliary tree (4). Laparoscopic ultrasound (LUS) has the advantage in its ability to scan target organs under direct vision due to direct contact with the organ of interest (14). The strategy of combining EUS with laparoscopy and LUS appeared to be cost-effective in detecting unresectable tumors and disseminated intra-abdominal disease in patients with digestive cancers, and more accurate than CT plus conventional trans-abdominal ultrasonography (16). A single-center study monitored the routine use of combined EUS and LUS and confirmed previous findings (17) indicating that this strategy is accurate for the pre-therapeutic evaluation of patients with cancers of the upper gastrointestinal tract.

During the last five years, NOTES has been gaining interest worldwide and many feasibility studies of different applications in visceral surgery have already been performed in experimental porcine models or even in humans (18-20). It was therefore a legitimate question whether EUS may play a role in NOTES. Elmunzer et al. (21) in a porcine model, studied the access through the anterior and posterior walls of the stomach, with or without EUS guidance, in terms of clinically relevant complications. Access without ultrasound guidance resulted in more frequent injuries to the liver and major blood vessels. The guided access was not devoid of complications, but there were fewer events (minor bleeding in two cases). Another comparative study performed by Fritscher-Ravens et al. (22) included 46 pigs, with 3 major complications (bleeding and organ injury, all during mediastinoscopy / thoracoscopy) occurring during the first 24 NOTES-alone procedures, while EUS-guidance enabled safe mediastinal or retroperitoneal access, with safe adrenal gland removal. However, EUS guidance seemed to offer no additional benefit in NOTES gastrojejunostomy procedures. The authors concluded from this experience, that EUS guidance might be useful for the initial access or to identify structures in anatomically difficult areas in NOTES procedures. These conclusions were also supported by the results in our study where EUS-guided access was safe for both the anterior, but also the posterior access to the pancreas. Moreover, the use of a linear EUS scope in the area posterior to the gastric wall was very useful to identify the pancreas. In addition, use of EUS guided tattoo placement in the pancreas and EUS guided T tag placement in the pancreas provided additional methods to assist in pancreatic localization.

Patients with pancreatic cancer may potentially benefit from staging using NOTES or EUS-NOTES, similar to the benefits described with laparoscopy combined with LUS (23). Small lymph nodes, liver and peritoneal metastasis may escape preoperative diagnosis workout even when accurate imaging procedures such as CT, MRI or even PET-CT are used. EUS-guided NOTES procedures might be very helpful in harvesting the lymph nodes that are most suggestive of harboring malignancy and used in conjunction with other imaging techniques available during EUS, eg. EUS elastography; these methods might prove additionally valuable for this. There are already some studies about lymph node mapping in colorectal cancer (24,25) and gastric cancer (26). EUS could thus identify lymph nodes susceptible of invasion, especially with elastography guidance, while direct excisional biopsy could be performed during NOTES (27).

A recent option in pancreatic cancer patients is represented by NOTES peritoneoscopy, performed through a transoral, transgastric route, with feasibility studies reported by the group at Ohio State University (28-33). One year later, the same group also reported the results of possible peritoneal bacterial contamination induced by the transgastric access, which proved that no infectious complications or leaks were noted at 30-day follow-up (29). In an extension of these two initial studies, the authors have shown that transgastric endoscopic (NOTES) peritoneoscopy is feasible for pancreatic cancer staging (30).

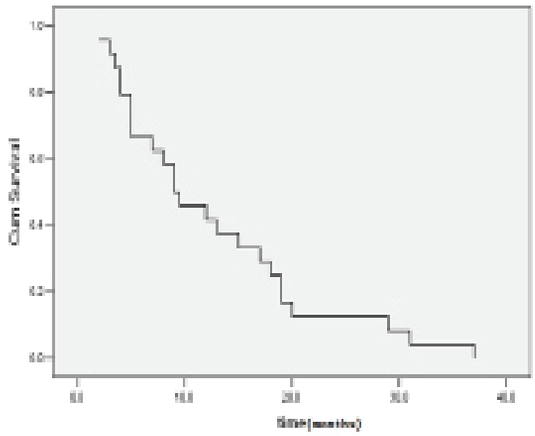
We, in our studies, investigated the use of EUS in NOTES approach to the pancreas that was not part of the protocols developed by the Ohio State University group (28-33). EUS provides the advantage of viewing beyond the GI wall and could potentially play an important role in safe access to the abdomen through the stomach by excluding vascular or other vital structures on the serosal side before gastric puncture and increasing the diagnostic and therapeutic possibilities with NOTES (21,22). As shown in our study, creation of an EUS guided fluid cushion, EUS guided tattoo of the pancreas and EUS guided pancreatic T tag placement, may increase the capabilities of NOTES beyond peritoneoscopy for pancreatic cancer staging to direct access to the pancreas for diagnosis and therapy. EUS provides excellent imaging of the pancreas and this may be important in selecting the site for gastric access closer to the area of interest (e.g. a small localized neuroendocrine tumor of the pancreas) We have shown in our study that an EUS-NOTES procedure performed through a posterior EUS-guided needle knife incision of the stomach wall with direct insertion of an endoscope in the omentalis bursa was very efficient in accurately accessing the pancreas for direct visual large-forceps biopsies. The posterior wall of the stomach could thus provide an excellent access to the pancreas in EUS-NOTES, while small tumors or cysts could potentially be identified with preoperative or intraoperative EUS and then enucleated under direct vision. Distal pancreatectomy has been performed in experimental models of NOTES (34,35), even in randomized trials in animal models that compared hybrid NOTES procedures and laparoscopic procedures (36). The results of a prospective randomized trial of these approaches indicated a small superiority of NOTES procedures, however with a longer time needed to perform the resection (36). Based on the initial results of our pilot study, the basis for a future survival study with a larger number of animals was established. There were no major complications for both EUS-guided anterior and posterior approaches except for a contralateral burn on the abdominal wall in the first animal with no bleeding (with all experts involved having major experience in therapeutic EUS procedures and one of the experts in additional experience in surgical procedures inside the abdomen). The limitations of our study include use of normal swine and not a large animal model (or patients) with pancreatic cancer, although much of the prior experimental NOTES and other endoscopic research in swine models has been done in non-diseased models as well. Other limitations include lack of survival data in this study.

In conclusion, pancreatic EUS-NOTES procedures are feasible. The role and place of EUS in pancreatic NOTES will be established only after adequate research and experience, and at that time, more indications will possibly be added to those presented and performed during our study. Randomized trials with and without EUS may need to be done for specific NOTES indications if benefits of EUS are not readily appreciable. We believe that EUS will play an important role in pancreatic NOTES procedures: for staging of pancreatic cancer; in the

TABLE 1. Description of the procedures performed in all eight pigs

Pig	Approach	Access	Accessories	Procedure	Closure	Complications
1	Anterior	EUS guided	Needle knife CRE balloon	Peritoneoscopy	Triclips	Contralateral burn on the abdominal wall
2	Posterior	EUS guided	19G EUS needle 0.035 guidewire needle knife CRE balloon	Retro-peritoneal space visualization: bowel loops covered by peritoneum but pancreas was never seen.	Prototype T-tags	none
3	Posterior	EUS guided	19G EUS needle 0.035 guidewire needle knife CRE balloon	Retro-peritoneal space visualization: bowel loops covered by peritoneum but pancreas was never seen.	No closure done	none
4	Anterior	Submucosal bleb creation	19G EUS needle 0.035 guidewire needle knife CRE balloon	Peritoneoscopy (bowel loops, liver and gall bladder seen) Successful gastrojejunostomy created	Prototype T-Tags	none
5	Posterior	EUS-guided Pancreas stained using GI spot	19G EUS needle 0.035 guidewire needle knife CRE balloon	Retro-peritoneoscopy Pancreas identified	No closure done	none
6	Posteriot	EUS-guided T tag deployed into pancreas	19G EUS needle 0.035 guidewire needle knife CRE balloon	Retro-peritoneoscopy: Liver pancreas, bowel loops and spleen identified. Direct pancreatic biopsies taken	No closure done	none
7	Anterior	EUS-guided	19G EUS needle 0.035 guidewire needle knife CRE balloon	Peritoneoscopy: liver, small bowel seen.	OTSC	none
8	Posterior	EUS-guided T tag deployed into pancreas	19G EUS needle 0.035 guidewire needle knife CRE balloon	Retroperitoneoscopy; Pancreatic tail dissection. Direct pancreatic biopsies	No closure done	none

palliative treatment of advanced pancreatic cancer patients; minimally invasive pancreatic procedures such as tumor enucleation as well as other targeted diagnostic and therapeutic procedures. We believe that EUS due to its many advantages with imaging and intervention has a potential to play an important role in pancreatic NOTES as more complex procedures are attempted beyond peritoneoscopy and should be investigated further as an important adjunct for NOTES.



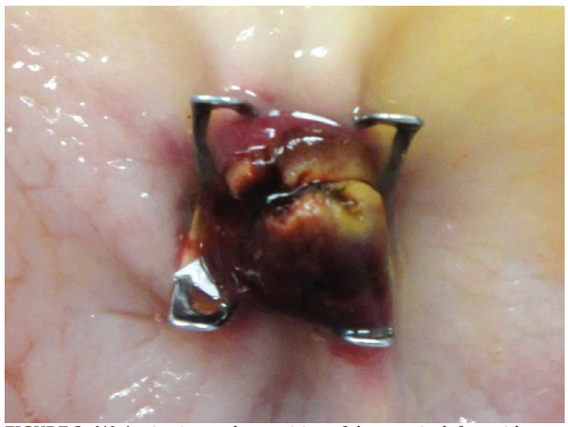


FIGURE 3. (A) Aspiration and apposition of the gastric defect with a special bi-forceps, followed by release of the OTSC clip in a manner very similar to a band ligation device; (B) The OTSC clip deployed in the pig stomach with safe closure of the gastric defect.

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