Feasibility of transgastric and transcolonic NOTES peritoneoscopy combined with intraperitoneal endoscopic ultrasonography

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Chapter 8

ABSTRACT

**Background:** If Natural Orifice Transluminal Endoscopic Surgery (NOTES) peritoneoscopy is to become an alternative to diagnostic laparoscopy, NOTES peritoneoscopy must be comparable to laparoscopy in its diagnostic accuracy.

**Objective:** To assess feasibility of transgastric (TG) and transcolonic (TC) NOTES peritoneoscopy combined with intraperitoneal EUS.

**Design:** Twelve nonsurvival experiments on 6 female pigs.

**Setting:** Animal laboratory

**Interventions:** Randomization was performed to determine order of approach (TG or TC as first procedure). After peritoneal access, systematic peritoneoscopy was performed according to a preassessed list of 12 locations considered clinically important. For each visualized location, 1 point was scored and 1 point added if touched as well, leading to a maximum score of 24 points. Subsequently, the endoscope was exchanged for linear echoendoscope. The percentage of visualization of the 4 sections of the liver was recorded (0: not visible; 1: 33%; 2: 66%; 3: 100%; maximum score, 12 points). After withdrawal the protocol was repeated using the 2nd natural orifice (TG or TC).

**Main outcome measurements:** Extent of adequate visualization of diagnostic peritoneoscopy and intraperitoneal EUS measured by a preassessed record form

**Results:** Access was achieved without difficulties at all 12 sites. TG peritoneoscopy resulted in a median of 23 points (range 20-24), via the TC approach the maximum of 24 points was recorded in all pigs (p=0.102). TG-EUS resulted in a median of 11 points (range 6-12) and TC-EUS in a median of 12 points (range 8-12) (p=0.317).

**Limitation:** Lack of objective landmarks

**Conclusions:** TG and TC NOTES peritoneoscopy combined with intraperitoneal EUS is technically feasible. Furthermore, NOTES peritoneoscopy and intraperitoneal EUS seems to result in adequate visualization of the peritoneal cavity and liver, respectively.
INTRODUCTION

Preoperative detection of peritoneal and other small intra-abdominal metastases of biliopancreatic and upper gastrointestinal malignancies can be difficult. Advances in preoperative imaging have improved detection and diagnosis of primary tumors, determination of Tumor (T) and lymph node (N) stage, and detection of metastases (M) as well.1, 2 However, small metastases and metastatic disease of the peritoneal surface are frequently missed and only detected at the time of surgery.3-8 Because the presence of metastatic disease is a contraindication for resection of the primary tumor in the majority of cases, laparoscopy and laparoscopic ultrasonography are frequently performed to exclude metastases before resection.

Natural Orifice Transluminal Endoscopic Surgery (NOTES) peritoneoscopy may become an alternative to laparoscopy. By avoiding abdominal incisions, NOTES has the potential to offer significant benefits to patients, such as less postoperative pain, decreased suppression of the immune system and thus enhanced postoperative recovery.9, 10 Furthermore, it could be performed as an outpatient procedure. The transluminal approach could be particular important for morbidly obese patients and others at high risk for complications of open and laparoscopic surgery.

In certain groups of patients, such as patients with periampullary and liver malignancies, laparoscopic ultrasonography has been shown to have additional value over laparoscopy alone and increases the yield of laparoscopy.3, 4, 8 If NOTES is to become an alternative to diagnostic laparoscopy it must be comparable from a diagnostic standpoint. However, until now there have been no reports on the use of intraperitoneal endoscopic ultrasonography (EUS) during NOTES procedures. The primary aim of our study was to assess feasibility of transgastric and transcolonic endoscopic peritoneoscopy combined with intraperitoneal EUS in a nonsurvival porcine model.

METHODS

Animals and preparation

Twelve nonsurvival experiments were performed on six 35- to 40-kg female pigs. Institutional review board approval was obtained from the local animal ethics committee. Animals were housed at the animal research facility at Academic Medical Hospital, University of Amsterdam, the Netherlands. The animals were fasted for 24 hours prior to the procedure. Pre-anaesthesia sedation consisted of ketamine (10mg/kg), midazolam (1mg/kg) and atropine (1ml/25 kg). General anaesthesia was achieved using 1% to 3% isoflurane. Analgesia consisted of continuous infusion of continuous intravenous infusion of sufentanil (2.5 μg/kg/h) (and if necessary additional bolus), pancuronium (1 mL/h) and midazolam (0,5-1,5 mg/kg/h).
Four hours before the procedure multiple enemas were administered until the distal colon was cleared from all particulate fecal matter. All experiments began with the animals in the supine position. To facilitate safe transluminal access to the peritoneal cavity, a Veress needle was placed for continuous carbon dioxide insufflation to create pneumoperitoneum at a pressure of less than 14 mmHg. All animals underwent peritoneoscopy plus EUS via both the transgastric (TG) and the transcolonic (TC) approach during which the pneumoperitoneum was maintained. Randomization was performed picking 1 of the 6 sealed envelopes to determine order of approach (TG or TC as first procedure).

**Transgastric approach**

After introduction of a double-channel endoscope (GIF 2T100; Olympus Corporation, Tokyo, Japan) into the stomach, internal indentation from abdominal palpation and/or installation of water was used to locate the anterior gastric wall. Two T–tags (Ethicon Endo-Surgery, Cincinnati, Ohio, USA) with attached sutures were placed flanking the margins of the planned incision site to facilitate subsequent closure. Gastric access was created by a needle knife (Cook Endoscopy, Winston-Salem, NC, USA) puncture followed by dilatation with an 18 mm CRE balloon (Boston Scientific, Natick, Mass, USA).

**Transcolonic approach**

After introduction of the therapeutic endoscope into the colon, residual stool was removed with aggressive washing and suctioning. Internal indentation from abdominal palpation and/or installation of water was used to locate the anterior colonic wall. At a distance of 15 to 20 cm from the anal verge, 2 T–tags were placed flanking the margins of the planned incision site to facilitate later closure. A focal colonic incision (< 2 to 3 mm) was created by using a needle knife with a brief pulse of coagulation and the endoscope was then slowly manoeuvred through the incision, enlarging it while moving through.

**Diagnostic Peritoneoscopy**

Systematic peritoneoscopy was performed according to a pre-assessed record form, which was based on locations considered clinically important. The 12 included locations were divided in 4 groups: Left and right peritoneal upper quadrants (2 structures), left and right hemidiaphragm (2 structures), liver and hepatoduodenal ligament (5 structures) and a miscellaneous group (3 structures: omentum, anterior stomach and duodenal curve). For each visualized location, 1 point was scored and 1 point added if the location had been touched with a biopsy forceps as well, resulting in a maximum score of 24 points. During the diagnostic procedure, the position of the animal was frequently changed to the Trendelenburg and anti-Trendelenburg to improve visualization. Endoscopic tools to improve visualization, such as an endoscopic forceps and application of a transparent cap, were used according to the endoscopists’ preference.
After the diagnostic procedure a standard 0.035-guidewire (Jagwire; Boston Scientific) was left in the peritoneal cavity, and the endoscope was exchanged for linear EUS-scope (GF-UCT140, Olympus). The guidewire was only used to visually guide the endoscopist as he introduced the echo-endoscope into the abdominal cavity. To facilitate estimation of the percentage of visualization, the porcine liver was divided in 4 sections (left and right superior and left and right inferior parts) by using endoscopy. These sections were systematically visualized. The extent of visualization of each section was assessed by the extent of visualization of the other side of the liver surface. In case the other side of the liver surface of the particular section was visualized in total, the entire section was estimated to be visualized. In case 66% (Fig. 1) or 33% of the other side of the liver surface was visualized, 66% and 33% of the section was, respectively, estimated to be visualized. For visualization of the entire section 3 points were scored, for approximately 66% of the section 2 (Fig. 1), and for approximately 33% 1 point, with a maximum score of 12 points. If it was not possible to adequately maneuver the EUS-scope on the section’s surface 0 points were scored. After withdrawal the entire protocol was repeated using the second natural orifice.

The gastrotomy and colotomy were closed using multiple T-tags or Resolution Clips (Boston Scientific) until the incision was macroscopically adequately closed. These closure techniques have frequently been applied in porcine NOTES experiments and have been described by others.11-19 The T-tag technique consists of a metal T-bar and thread loaded in a 19 gauge hollow needle, which is passed through the tissue a few millimetres from the defect. After ejecting the anchor beyond the wall, another T-tag is placed on the opposite side of the incision. Consequently the threads are tied together with a locking cinch.

After closure, the animals were euthanized and the abdominal cavity was grossly inspected post-mortem for signs of bleeding or perforation. The gastric and colonic closure sites were examined in detail and checked for air tightness. Air tightness was checked by clamping the duodenum or proximal part of the colon, respectively, and insufflation of air using a syringe. During this leak test the closed gastrotomy or colotomy was held submersed to visualize air bubbles in case of leakage.

**Fig. 1** EUS image showing an example of the EUS scoring system. In this case, the extent of visualization of a particular section was estimated at 66% based on the extent of visualization of the other side of the liver surface.
Outcome parameters and statistics

The primary outcome parameters were the extent of adequate visualization of endoscopic diagnostic peritoneoscopy and extent of adequate visualization of the liver by intraperitoneal EUS measured by a preassessed record form. Secondary outcome parameters were safety of access, procedural time (starting from introduction of the (echo)endoscope into the peritoneal cavity until removal from the peritoneal cavity) and reliability of closure. Safety of access was defined as the absence of bleeding and laceration or perforation of visceral organs. Reliable closure was defined as the absence of air leakage during insufflation of the closed gastrotomy or colotomy. All calculations were carried out using the Statistical Package for Social Sciences for Windows 12.0.1 software package (SPSS Inc, Chicago, IL, USA). Quantitative data are expressed as median plus range. Statistical significance was assessed by using the paired Wilcoxon signed rank tests.

RESULTS

Peritoneal access was achieved without complications at all 12 sites (6 TG, 6 TC). In 3 pigs, experiments started with the TG approach. The per-pig results are summarized in table 1. According to the preassessed record form, the TG peritoneoscopy resulted in a median score of 23 points (range 20-24); by using the TC approach, the maximum of 24 points was recorded in all pigs (p=0.102). In all 12 experiments (TG and TC), the peritoneal and diaphragm quadrants, omentum, anterior stomach and duodenal curve could be adequately visualized and touched with a biopsy forceps. In 3 of 6 TG and all TC experiments the whole liver surface and hepatoduodenal ligament were adequately visualized (Fig. 2). In all these experiments, a transparent cap was used to adequately visualize the inferior surface of the liver and the hepatoduodenal ligament (Fig. 3). In the remaining 3 experiments using the TG approach, despite the use of a transparent cap, it was not possible to adequately visualize the liver surface. In detail, in one TG

### Table 1: Diagnostic points scored per pig according to the preassessed record form

<table>
<thead>
<tr>
<th>Pig</th>
<th>Total TG peritoneoscopy (max 24)</th>
<th>Total TC peritoneoscopy (max 24)</th>
<th>Total TG intraperitoneal EUS (max 12)</th>
<th>Total TC intraperitoneal EUS (max 12)</th>
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TG: Transgastric; TC: Transcolonic; max: maximum
experiment, the hepatoduodenal ligament was missed; in another the right inferior part of the liver was missed; and in a third TG experiment the right inferior part and the ligament were missed.

TG-intraperitoneal EUS resulted in a median of 11 points (range 6-12) and TC intraperitoneal EUS in a median of 12 points (range 8-12) (p=0.317). In 4 of 6 pigs, the entire liver was estimated to be recorded in total by using the TG and TC approach (Fig. 2). In 2 pigs it was not possible to visualize the entire liver. In one pig 50% and in another 33% of the liver was estimated to be missed during TG EUS. TC intraperitoneal EUS resulted in missed areas of, respectively, 33% and 17% in the same 2 pigs (Table 1). In these 2 pigs, it was also not possible to visualize the inferior surface of the liver during TG peritoneoscopy.

The median procedural time of the TG and TC peritoneoscopy from entering the peritoneal cavity was, 10 (range 7-15) and 10 minutes (range 4-12) respectively. Median TG intraperitoneal EUS time was 9 minutes (range 4-22) and TC intraperitoneal EUS 7 (range 6-10). These differences were not significantly different (p=0.221 and p=0.655 respectively).

In the first 2 experiments the gastrotomy and colotomy closure was attempted using Resolution clips (median of 5 and 4 respectively). In 1 animal, the gastrotomy could not be completely closed with endoclips due to edema at the incision site. At necropsy 0/2 gastrotomies and 1/2 colotomies were airtight. In latter 4 experiments the gastrotomy and colotomy were closed with a median of 6 (range 6-8) and 6 (range 4-8) T-tags, respectively. Closure of the gastrotomy and colotomy was achieved macroscopically successfully in all experiments (Fig. 4). At necropsy, 2 of 4 gastrotomies and 3 of 4 colotomies were airtight. At necropsy, there were no signs of bleeding. In 2 cases injury
of adjacent organs due to transluminal blind puncture of the T-tags was seen. In 1 case, the small bowel was attached to the closed colotomy, and in another case, the colotomy was fixed to the abdominal wall.

DISCUSSION

Adequate staging of upper gastrointestinal tumors is crucial when determining the appropriate medical or surgical therapy. The main goal of laparoscopic staging for patients with gastrointestinal malignancies is to avoid laparotomy in patients with incurable disease. To minimize the invasiveness of peritoneal access further, the next step would be to avoid the anterior abdominal wall approach completely. Since the introduction of NOTES, the feasibility of NOTES peritoneoscopy has been demonstrated in several reports, including one human case series. To cover the whole range of diagnostic possibilities of laparoscopy, we took this concept one step further and showed the feasibility of transluminal intraperitoneal EUS. In 8 of 12 experiments, the entire liver was visualized with intraperitoneal EUS. Although intraluminal EUS has been shown to be a useful tool in visualizing the liver, it cannot reach all parts of the liver by intraluminal gastroduodenoscopy. Furthermore, considering the currently increasing indications for therapeutic intraluminal procedures under EUS guidance, EUS could be useful for intraperitoneal therapeutic procedures as well.
Besides the feasibility of intraperitoneal EUS, this study demonstrated compelling results of transluminal NOTES peritoneoscopy. All the predetermined abdominal structures could be visualized and touched during the TC NOTES peritoneoscopy, and 83% could be visualized via the TG approach. Because a scoring system to assess the capability of NOTES peritoneoscopy did, to our knowledge, not yet exist, it was constructed based on the clinical important locations. This report is the first to evaluate NOTES peritoneoscopy according to a predetermined standardized record form to improve objective analysis of the collected data.

Until now, all studies reports in literature, except one, concerning diagnostic NOTES peritoneoscopy used the TG approach. The TG approach, however, often resulted in limited visualization of structures in the upper abdomen. Difficulties in visualizing the gallbladder and the right lobe of the liver via the TG approach were confirmed in the first human NOTES case series and are therefore not confined to pig anatomy. Therefore, the TG and TC approach were evaluated in this study. Furthermore, this is the first report in which the TG and TC approach were evaluated in a paired model. In all 12 experiments (TG and TC), all structures, apart from the liver, could be adequately visualized and touched during NOTES peritoneoscopy. Using the TG approach, it was not possible to visualize the inferior part of the liver in half (3 of 6) of the experiments. Because of the relatively short length of the bending section of the endoscope, the right lateral part of the liver was out of reach during maximal deflection of the endoscope. Improved endoscope design that allows a larger bending section or second bending section, such as the R-scope (Olympus), could improve this limitation. A steerable overtube driving the scope in retroflexion may overcome this hurdle as well. However, the decreased stability and difficulty in orientation of working in retroflexion remain and may also present problems in a human setting (Fig. 2).

In contrast, with the TC approach, all structures were adequately visualized, and structures in the upper abdomen could be easily reached en face. By avoiding the need for retroflexion, endoscope stability increased as well. Although this pilot study was underpowered to detect a difference in upper abdomen visualization between these two approaches, our results suggest superiority of the TC approach. The potential higher risk, however, of peritoneal contamination by using the TC approach should not be overlooked. In these nonsurvival experiments peritoneal contamination was not measured. Survival animal studies are required to further evaluate the potential advantages and risks of the TC approach.

The 2 pigs, in which parts of the liver were missed during intraperitoneal EUS were the same 2 pigs in which the inferior surface was partially missed during TG peritoneoscopy (Table 1). This may be explained by per-animal variance in abdominal anatomy. In particular, the size of the spleen varied per animal; in one of these 2 pigs, the spleen covered a large part of the liver, making adequate visualization difficult.
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By using a preassessed record form, objective interpretation of the collected data was attempted as much as possible. However, it remained difficult to measure whether the target structure was completely visualized. During intraperitoneal EUS especially, visualization was rather subjective since objective landmarks were missing. Studies with more objective endpoints, for example by prior placement of hyperdense markers, are required to further evaluate the diagnostic yield of intraperitoneal EUS. Comparative studies of NOTES peritoneoscopy and the gold standard, diagnostic laparoscopy, are required as well.

Closure of the access site has been studied extensively in other reports\textsuperscript{13-15, 17-19, 28, 34-36} and was a secondary objective in this NOTES peritoneoscopy feasibility study. In the first 2 pigs, closure was attempted using Resolution clips. However, because of widely spaced incision edges and tissue edema, closing the incision with standard Resolution clips proved to be challenging.\textsuperscript{15} Therefore the other 8 access sites were closed using T-tags. Although T-tags have frequently been used in porcine NOTES experiments\textsuperscript{11-13, 16, 18} and even in a few human cases\textsuperscript{37}, initial results in this relatively small nonsurvival study were unsatisfactory. A considerable part of the closed gastrotomies and colotomies using T-tags did not result in adequate insufflation without air leakage of the stomach and colon, respectively. Although we used a rough, non standardized method for leak testing and had relatively less experience with in vivo T-tag closure, these results match the results of an ex vivo burst pressure study evaluating different gastrotomy closure modalities.\textsuperscript{36} Furthermore, blind puncturing through the gut wall may lead to injury of adjacent organs.\textsuperscript{13, 38} In 2 cases, the colotomy was stitched to the abdominal wall and small bowel. Although it must be realized that outcome of T-tag closure may have been better in experienced hands\textsuperscript{11, 13, 16, 18, 37}, other NOTES closure modalities seem to result in more reliable and safe closure and seem to be better candidates for future survival studies.\textsuperscript{28, 35, 36, 39}

In conclusion, we have shown the feasibility of NOTES peritoneoscopy combined with intraperitoneal EUS. Furthermore, NOTES peritoneoscopy and intraperitoneal EUS seems to result in adequate visualization of the peritoneal cavity and liver, respectively. Survival and randomized studies comparing NOTES peritoneoscopy with diagnostic laparoscopy are required to further evaluate the potential of this novel technique.
REFERENCES


Feasibility of transgastric and transcolonic NOTES peritoneoscopy


