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EDITORIAL

Natural orifice transluminal endoscopic surgery in pancreatic diseases

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Abstract

Natural orifice transluminal endoscopic surgery (NOTES) is a surgical technique that has received considerable interest in recent years. Although minimal access surgery has increasingly replaced traditional open abdominal surgical approaches for a wide spectrum of indications, in pancreatic diseases its widespread use is limited to few indications because of the challenging and demanding nature of major pancreatic operations. Nonetheless, there have been attempts in animal models as well as in the clinical setting to perform diagnostic and resectional NOTES for pancreatic diseases. Here, we review and comment upon the available data regarding currently analyzed and performed pancreatic NOTES procedures. Potential indications for NOTES include peritoneoscopy, cyst drainage, and necrosectomy, palliative procedures such as gastroenterostomy, as well as resections such as distal pancreatectomy or enucleation. These procedures have already been shown to be technically feasible in several studies in animal models and a few clinical trials. In conclusion, NOTES is a rapidly developing concept/technique that could potentially become an integral part of the armamentarium dealing with surgical approaches to pancreatic diseases.

Key words: Natural orifice transluminal endoscopic surgery; Pancreatic disease; Chronic pancreatitis; Pancreatic resection; Pancreatic drainage

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INTRODUCTION

Flexible endoscopy has traditionally been limited to the intestinal lumen. However, in recent years various attempts to also provide endoscopic access to the peritoneal cavity for diagnostic and therapeutic procedures have been made. Two novel developments in gastrointestinal endoscopy and surgery have facilitated these attempts: (1) the establishment of endoscopic retrograde cholangiopancreatography in the 1970s and endoscopic ultrasound in the 1980s offered gastrointestinal endoscopists not only purely diagnostic but also therapeutic options; and (2) simultaneously, minimal access surgery increasingly replaced traditional open abdominal surgical approaches for a wide spectrum of indications. These developments led to a new and innovative, interdisciplinary way of accessing the

peritoneal cavity through the natural orifices of the body by means of transluminal endoscopic approaches to the abdominal cavity: natural orifice transluminal endoscopic surgery (NOTES). These new techniques avoid the need for abdominal incisions and may offer potential benefits, such as being less invasive and possibly more cost-effective than the traditional open or laparoscopic surgery for certain indications. In addition, NOTES may offer specific advantages for selected patient populations. For example, this technique seems especially relevant to those patients with high surgical risk, e.g. the morbidly obese patient or patients with multiple prior abdominal interventions or surgical wound infections. Since the method was first described by Kalloo *et al*[1] in 2004, surgeons and gastroenterologists have worked on transluminal access and intraabdominal surgical procedures[2].

In America and Europe, collaborative organizations of surgeons and gastroenterologists, the Natural Orifice Surgery Consortium for Assessment and Research™ (NOSCAR™)[3] and the EURO-NOTES Foundation (www.euro-notes.org), have been established to encourage and document the further development of NOTES. However, before establishing this new method and bringing it into general clinical practice, it must be confirmed to be safe and to provide real advantages for patients, thus avoiding the mistakes that were made when laparoscopic surgery was introduced a few decades ago. Therefore, the American Society for Gastrointestinal Endoscopy (ASGE) and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Working Group met in 2006 to define in a white paper the hurdles and challenges (e.g. safe methods for closure of the gastric incision, avoidance of infections, *etc*.) to be addressed in the coming years[4].

The first experimental laparoscopy was reported in 1901 by the German surgeon Georg Kelling[5], who insufflated gas into the abdomen of dogs, but it was only 84 years later in 1985 that Erich Mühe performed the first laparoscopic cholecystectomy. Since this was rejected by the German Surgical Society, it took another two years until the French gynecologist, Philippe Mouret, reported a laparoscopic cholecystectomy with only four trocars, and that event finally triggered the interest in modern minimal access invasive surgery[6]. However, in the years that followed, many barriers to laparoscopic surgery had to be overcome. Critical elements of a new surgical technique include the development of appropriate instrumentation, requiring collaboration of medical professionals, engineers and the industry. Learning from the introduction of laparoscopic surgery, NOTES should only be implemented if all important aspects including feasibility and safety have been sufficiently evaluated, and indications have been clearly defined[7].

Training performed in a clean and safe environment, with performance analysis generating learning curves, improves patients' safety and outcomes and maximizes the benefits of implementation of new procedures such as NOTES[8]. Besides animal laboratory training, newly developed training phantoms for NOTES have been described[9].

Despite these important issues, NOTES techniques have developed rapidly over the past few years, mainly due to a close collaboration between surgeons and gastroenterologists and extensive experimental animal research. Multiple trials regarding the different access sites to the peritoneal cavity and endoscopic interventions in the abdomen have been described. The basic experience with this new procedure has been largely with animal studies; human case reports are rare, but the number is increasing steadily.

Using NOTES, surgeries like cholecystectomy[10,11], gastrojejunostomy[10,12], antireflux surgery[13], appendectomy[14], and splenectomy[15], as well as several gynecologic procedures including tubal ligation[16], oophorectomy[17] and partial hysterectomy[17], have been performed successfully in animal models *via* different approaches such as transgastric/transcolonic/transvaginal using current commercial endoscopes. Retroperitoneal interventions such as nephrectomy have also recently being described[18].

PURE OR HYBRID NOTES

According to the NOSCAR committee, pure NOTES is defined as flexible endoscopic procedures performed by crossing the respective lumen[5,19]. Natural orifices to the abdominal cavity that are actually used are the transgastric route (*via* the mouth), the transvaginal route, the transsigmoidal access *via* the anus, and the transurethral path. The use of single port surgery for percutaneous access is viewed controversially, and considered only if flexible endoscopes are used. The use of rigid instruments and even transanal endoscopic micro-surgery (TEM) are not considered as pure NOTES procedures.

Some difficulties result from these access sites as follows; firstly: penetrating the transluminal barrier with the endoscope, secondly: avoidance of contamination of the abdominal cavity, and thirdly: the closure of the entrance point. Once having passed the transluminal barrier further challenges arise. Intraoperative manipulations are possible but often limited by the unidirectional force exertion, the lack of haptic and tactile sensations and the limited triangulation with just one instrument. Medical scientists, engineers and industrial companies are working on various solutions, such as double channel endoscopes and bending instruments. Finally, the closure of the transluminal entrance has to be assured. This seems to be easier with the transvaginal and transurethral routes (which are also less prone to contamination) than with transgastric or transsigmoidal access. Nevertheless, all routes have their specific difficulties. Potential advantages of this new technique are the lack of incisional problems, e.g. pain, hernia, wound infections, as well as less adhesions and better cosmetic results.

Hybrid NOTES procedures include endoscopic surgery with the aid of laparoscopic vision or instruments for operation or access closure. The hybrid technique is actually the most commonly used form. Pure NOTES interventions are rare, and thus hybrid NOTES may serve as a temporary approach to further develop pure NOTES techniques. Parallel to the NOTES working group, the

New European Surgical Academy (NESA) founded the interdisciplinary working group for Natural Orifice Surgery (NOS) to develop surgical procedures using the natural body openings, e.g. by using a new surgical instrument, the Transdouglas Endoscopic Device (TED), a flexible multichannel instrument enabling single-entry "scarless" operations[20]. Whether pure NOTES, hybrid procedures or NOS, all these techniques are expected to move forward towards a less invasive surgical discipline.

The role of NOTES in pancreatic diseases has been analyzed in a relatively small number of experimental and clinical studies[21]. NOTES procedures might play a potential role in the diagnosis and therapy of pancreatic diseases, specifically in those areas where endoscopic and/or laparoscopic approaches have already been established, and are - at least in some centers - part of the clinical routine.

CURRENT SURGICAL PROCEDURES FOR PANCREATIC DISEASES

Open pancreatic surgery

There are various surgical procedures available for different pancreatic diseases. Resections include pancreatic head resections (classical, pylorus-preserving and duodenum-preserving partial pancreatoduodenectomies), segmental resections, distal resections, total pancreatectomies, enucleations and others. In addition, palliative procedures such as biliodigestive anastomosis and gastric bypass procedures are frequently carried out, as well as special procedures such as necrosectomy or pancreatic pseudocyst drainage (cysto-gastrostomy or cysto-jejunostomy). Open pancreatic surgery is still the gold standard but is now being challenged by endoscopic or laparoscopic approaches for a number of indications as discussed below.

Diagnostic approach for pancreatic tumors

Diagnostic laparoscopy has a limited role in potentially resectable tumors to evaluate local resectability, and to exclude distant metastases. In addition, in patients with locally non-resectable tumors who are scheduled for neoadjuvant therapy, laparoscopy is generally recommended to confirm diagnosis and to rule out occult metastasis[22,23].

Endoscopic treatment of pancreatic diseases

Endoscopic retrograde cholangiopancreatography (ERCP) offers a number of options in the diagnosis and management of pancreatic and biliary duct obstruction. However, ERCP as a diagnostic measure has been replaced to a large extent by modern imaging, e.g. MRI/MRCP. In addition, biliary or pancreatic duct drainage has a limited role in pancreatic and biliary diseases, being mostly restricted to the palliative setting. The development of endoscopic ultrasonography (EUS) offers further diagnostic accuracy for some pancreatic diseases, e.g. small tumors, neuroendocrine or cystic lesions/tumors. Nonetheless, there have been several novel therapeutic applications requiring an endoscopic approach. To cite an example, endoscopic ultrasound-guided celiac plexus block or pancreatogastrostomy and pancreatobulbostomy with stent insertion into the pancreatic duct for pain relief in patients with chronic pancreatitis[24,25]. Even procedures targeting pancreatic tumors with radiofrequency ablation[26], photodynamic therapy[27], and brachytherapy[28] using an endoscopic approach have been recently described in pilot studies. However, while there is a clear trend towards development of novel endoscopic procedures in the therapy of pancreatic diseases, evidence-based data are mostly lacking, and if present, point towards a more surgical approach, at least for some indications[29].

Laparoscopic pancreatic surgery

Drainage and necrosectomy: Internal drainage of pancreatic pseudocysts can be accomplished by traditional open or minimal access laparoscopic or endoscopic approaches. Minimal access surgery to drain pseudocysts can be performed with comparable morbidity and has become the standard of care in many cases; endoscopic approaches have similar success rates[30,31]. Open surgical necrosectomy for the treatment of infected pancreatic necrosis has relatively high morbidity and mortality rates; therefore minimal access laparoscopic as well as endoscopic or radiologic approaches are more commonly being used nowadays[32].

Bypass operations: Open (versus laparoscopic) gastrojejunostomy has been the standard palliative treatment in patients with unresectable pancreatic cancer with gastric outlet obstruction. It has a good functional outcome and relieves symptoms in many patients (if the patients were not treated by prior endoscopic stent therapy). Laparoscopic gastrojejunostomy has nowadays been proven as an effective palliation with rapid recovery in these advanced cases. Even transumbilical single-incision laparoscopic anastomoses have been reported as feasible and safe[33].

In cases of biliary obstruction (and in the case when endoscopic stent placement is not the treatment of choice), open biliodigestive anastomosis (hepaticojejunostomy) *vs* double bypass surgery (biliodigestive anastomosis and gastric bypass) has been a topic of discussion. However, laparoscopic hepaticojejunostomy is a relatively complex surgical procedure and only few reports are available for adult patients[34,35].

Laparoscopic pancreatic resections

Distal pancreatectomy: Laparoscopic distal pancreatectomies with or without preservation of the spleen have been performed and described since 1996[36]. The available data confirm that laparoscopic distal pancreatectomies are safe operations with similar or shorter operative times, blood loss, complication rates, and length of hospital stay for benign or noninvasive lesions of the pancreas in experienced hands[37,38]. As long as the resection margins are negative and the lymph node clearance is within accepted standards, this can also be performed for malignant lesions. Even though laparoscopic distal pancreatectomies are safe and feasible, most centers still carry out this resection as an open procedure[36].

Enucleation of pancreatic lesions: Laparoscopic enucleation of smaller lesions, especially with regard to neuroendocrine tumors, has also been described to be a feasible and safe approach[39]. It is associated with reduced postoperative hospital stay and comparable rates of pancreatic fistula in comparison to open surgery, although controlled trials and larger series are lacking to support these early observations.

Pancreaticoduodenectomy: Despite their early description by Gagner *et al*[40] in 1994, partial pancreaticoduodenectomies are considered extremely technically demanding for the laparoscopic approach. Recently published analyses describe laparoscopic partial pancreaticoduodenectomy as feasible, safe, and effective. Performed by highly skilled surgeons, even malignant lesions can be resected with negative margins and adequate lymph node dissection[41]. On this background, it remains to be seen whether laparoscopic pancreaticoduodenectomy can become the new surgical standard in the years to come[42].

NATURAL ORIFICE TRANSLUMINAL ENDOSCOPIC SURGICAL INTERVENTIONS IN PANCREATIC DISEASES

Diagnostic

Transgastric diagnostic endoscopic peritoneoscopy has been proven to be safe and feasible[43]. The first human clinical trial was performed on a group of ten patients with pancreatic masses. In four of these cases, peritoneal or liver biopsies were taken. Clinically significant contamination of the peritoneal cavity from the transgastric route was not observed[44]. In a recent study, 20 patients underwent laparoscopy and afterwards transgastric endoscopic peritoneoscopy, with comparable results for both procedures in 19 of 20 patients[45]. Safe and reliable gastric closure is now perhaps the only limitation to routine clinical implementation of this approach.

Therapeutic-non resection

Drainage and necrosectomy: In recent decades many interventional attempts to improve symptoms of chronic pancreatitis have been performed, such as decompression of the pancreas by stenting or stone extraction, as well as evacuation and drainage of pseudocysts. Endoscopic cystogastrostomy and cystoduodenostomy are important steps towards pure NOTES interventions[46]. In the reported case of a seven-year-old child, a hybrid NOTES cystogastrostomy was performed successfully through an existing gastrocutaneous fistula[47].

Therapy of necrotizing pancreatitis has changed in recent decades. Open approaches have increasingly been replaced by minimal access necrosectomies[48]. Minimal access approaches are often performed *via* an endoscopic transgastric access and therefore these procedures build the bridge to NOTES[49]. Indeed, transgastric/transduodenal necrosectomy has been carried out successfully in a number of studies with good long-term maintenance of the initial success and this approach has arguably been termed a currently practiced NOTES procedure[50].

Bypass operations: There have been no reports regarding pure NOTES operations for gastric and/or biliary bypasses. Hybrid NOTES for Roux-en-Y gastric bypass has been shown to be technically feasible in human cadavers[51].

EUS-guided therapeutic strategies in the therapy of pancreatic lesions: The EUS-guided injection of different substances seems to be a potential therapeutic option for cystic and also malignant pancreatic lesions. For example, the injection of ethanol into the pancreas in a swine model has been described and resulted in a localized concentration-dependent tissue necrosis without complications, which might arguably be used in the therapy of cystic lesions of the pancreas[52]. EUS-guided photodynamic therapy (PDT) with photosensitizing agents, as well as radio frequency ablation, has been shown to be safe and effective in ablation of pancreatic tissue, achieving local pancreatic tissue destruction[26,53]. EUS-guided injection of paclitaxel provided high and sustained localized concentrations in the porcine pancreas, leading to the assumption that this technique might be a potential minimal access therapeutic option for unresectable pancreatic tumors[54].

Therapeutic-resection

Distal pancreatic resections: Ryou *et al*[55] demonstrated in 2007 the technical feasibility of hybrid NOTES distal pancreatectomy in five pigs, and Matthes *et al*[56] demonstrated the feasibility of a pure NOTES distal pancreatectomy also in 2007. Allemann *et al*[57] reported on the initial experience in five pigs using a transvaginal retroperitoneal NOTES approach for distal pancreatectomy without any intraoperative complications. In a first randomized controlled trial of NOTES *vs* laparoscopic distal pancreatectomy in a porcine model, Willingham *et al*[58] demonstrated that there were no clinical or survival differences between NOTES and laparoscopy, although the laparoscopic operations were significantly faster (Table 1).

Enucleation of pancreatic lesions and partial pancreaticoduodenectomy: Only one actual study has been carried out concerning the feasibility of pancreatic tumor enucleation *via* a transgastric route in a porcine model[59]. No animal or human NOTES partial pancreaticoduodenectomies have currently been reported in the literature.

CONCLUSION

Transgastric/transduodenal drainage of pancreatic pseudocysts as well as necrosectomies are performed regularly in humans and have been shown to be safe and feasible, with a potential clinical benefit. Transgastric diagnostic peritoneoscopy for the staging of pancreatic cancer is also safe and feasible, and has been experimentally performed in humans. Pancreatic left resections, tumor enucleations and EUS-guided application of radiofrequency ablation,

Table 1 Pancreatic resections *via* natural orifice transluminal endoscopic surgery

	Yr	Access	Operation	Model	*n*	Type of study	Pure NOTES
Matthes *et al*[56]	2007	Transgastric	Distal pancreatectomy	Swine	6	Feasibility, nonsurvival	+
Ryou *et al*[55]	2007	Transcolonic/transvaginal	Distal pancreatectomy	Swine	5	Nonsurvival (3), survival (2)	-
Willingham *et al*[58]	2009	Transgastric	Distal pancreatectomy	Swine	28	Survival	-
Allemann *et al*[57]	2009	Transvaginal	Distal pancreatectomy	Swine	5	Nonsurvival	+

NOTES: Natural orifice transluminal endoscopic surgery.

photodynamic therapy or application of chemotherapeutics seems to be feasible in porcine models. The oncological outcome of these interventions remains unclear. Biliary and/or gastric bypass operations, as well as partial pancreaticoduodenectomies, have rarely or never been performed using NOTES either in animal models or in humans.

In summary, NOTES may play an increasing role in the drainage of pancreatic pseudocysts and in necrosectomy, in the staging of pancreatic masses and also in the palliative treatment of unresectable pancreatic tumors. Other minimal access pancreatic procedures may be a long-term aim in ongoing development. It is obvious that technical issues, including instrumentation, visualization, intra-abdominal manipulation and gastric closure need further refinement.

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