

## Current developments in natural orifices transluminal endoscopic surgery: An evidence-based review

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### Abstract

Tremendous advances have been made in recent years addressing the key obstacles to safe performance and introduction of human natural orifice transluminal endoscopic surgery (NOTES). Animal studies have focused on identifying optimal solutions to these obstacles, in particular methods of creating transluminal access, safe closure of the point of access, and development of a multitasking platform with dedicated instruments. Whether the performance data generated from these animal studies can be reproduced in humans has yet to be determined. Reports of human NOTES procedures are emerging, and the possibility of accomplishing human NOTES based on existing technology has been demonstrated. However, dedicated platforms and devices are still lacking to allow for pure NOTES procedures, and whether NOTES can deliver the postulated benefits of earlier recovery and improved cosmesis remains uncertain.

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**Key words:** Natural orifice transluminal endoscopic sur-

gery; Endoscopic surgery; Minimally invasive surgery; Vaginal surgery

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### INTRODUCTION

The natural orifice transluminal endoscopic surgery (NOTES) white paper released in 2005 stated that a number of key issues had to be overcome before NOTES could be fully implemented in human subjects<sup>[1]</sup> (Table 1). Since then, there has been an exponential growth in the number of NOTES-related publications in the literature, from less than 10 articles in 2006 to over 180 in 2009 (through a PubMed search). NOTES has been demonstrated to be a feasible approach for the performance a wide variety of procedures in animal studies, and reports of human studies are emerging<sup>[2-16]</sup>. This paper aims to provide an evidence-based review of the current developments in NOTES, with particular emphasis on recent advances in tackling the key obstacles, and to provide an update on the latest development in human NOTES procedures.

## METHODS

### Search strategy

Studies were identified by performing electronic searches of MEDLINE, EMBASE, Current Contents, the Cochrane Library, and Entrez PubMed from January 2000 to January 2010. The search terms “natural orifice” or “transluminal or transluminal” and “endoscopy or endoscopic surgery or surgery” were used. Additional articles were identified by a manual search of the references in key articles. Amongst the identified studies, articles in English describing randomized controlled trials (RCTs) were considered first. In areas with limited or no RCTs, nonrandomized comparative studies and case series were also included. Only fully peer-reviewed articles were selected.

### Inclusion and exclusion criteria

Only studies reporting the outcomes of NOTES-related procedures or devices were selected. Case reports were excluded except in human studies, where only a limited selection of studies was available.

## ANIMAL STUDIES

### Methods of access to the thoracic or peritoneal cavity

The thoracic and peritoneal cavity can be accessed by the transluminal approach and the method of transluminal access represents the first barrier to NOTES. In mediastinal/thoracic NOTES, the only site of access is through the thoracic esophagus. While for the abdominal cavity, NOTES accesses can be made *via* the transgastric, transcolonic, transvaginal, or transvesical approach.

Note that the thoracic esophagus is surrounded by a number of critical structures, including the descending thoracic aorta, the azygous vein, the pulmonary veins, and the heart. Locating a point of safe access is of paramount importance to avoid catastrophic vascular complications. Endoscopic ultrasound (EUS) has been shown to be a valuable tool for locating sites of safe accesses<sup>[17-19]</sup>. In the mediastinum, EUS can help identify landmarks such as the aortic arch, which facilitates optimal entrance sites for forward-viewing exploration and intervention<sup>[17]</sup>.

With the site of entry located, one then needs to consider the method of creating a transluminal incision. In early transgastric NOTES procedures, published by Kalloo *et al.*<sup>[20]</sup> and other authors between 2004 and 2005, the majority of transgastric gastrotomies were created by a needle-knife, followed by progressive enlargement of the incision using a pull-type sphincterotome or dilating balloon<sup>[20-24]</sup>. Both methods are effective ways of creating a transgastric gastrotomy. Nevertheless, using the sphincterotome is quicker than balloon dilation, and it also prevents spontaneous closure of the gastrotomy<sup>[22]</sup>. Thus, the sphincterotome method is more advantageous if repeated gastric crossing is required. In an attempt to further improve the ease of creating direct transgastric accesses, a prototype one-step needle sphincterotome has been

Table 1 Summary of human natural orifice transluminal endoscopic surgery procedures

Authors	Type of procedure	No. of patients	Organ of access
Marescaux <i>et al.</i> <sup>[21]</sup> (2007)	Cholecystectomy	1	Transvaginal
Zorrón <i>et al.</i> <sup>[3]</sup> (2007)	Cholecystectomy	1	Transvaginal
Gettman <i>et al.</i> <sup>[4]</sup> (2007)	Peritonoscopy	1	Transvesical
Hazey <i>et al.</i> <sup>[5]</sup> (2008)	Peritonoscopy	10	Transgastric
Lacy <i>et al.</i> <sup>[6]</sup> (2008)	Sigmoidectomy	1	Transvaginal
Ramos <i>et al.</i> <sup>[7]</sup> (2008)	Sleeve gastrectomy	1	Transvaginal
Zorrón <i>et al.</i> <sup>[8]</sup> (2008)	Peritonoscopy	1	Transvaginal
Zornig <i>et al.</i> <sup>[9]</sup> (2009)	Cholecystectomy	68	Transvaginal
Decarli <i>et al.</i> <sup>[10]</sup> (2009)	Cholecystectomy	12	Transvaginal
Gumbs <i>et al.</i> <sup>[11]</sup> (2009)	Cholecystectomy	4	Transvaginal
Auyang <i>et al.</i> <sup>[12]</sup> (2009)	Cholecystectomy	1	Transgastric
Horgan <i>et al.</i> <sup>[13]</sup> (2009)	Cholecystectomy	1	Transvaginal
Kaouk <i>et al.</i> <sup>[14]</sup> (2009)	Nephrectomy	1	Transvaginal
Fischer <i>et al.</i> <sup>[15]</sup> (2009)	Sleeve gastrectomy	1	Transvaginal
Lacy <i>et al.</i> <sup>[16]</sup> (2009)	Sleeve gastrectomy	1	Transvaginal

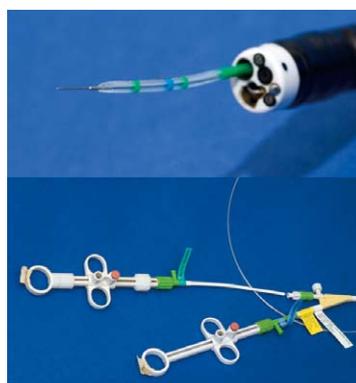


Figure 1 The one-step needle sphincterotome.

developed by the authors' unit (Figure 1)<sup>[25]</sup>. The instrument consists of a retractable needle knife and a pull-type sphincterotome on the same instrumental shaft, which allows extension of the gastrotomy incision created by the needle knife without the need of changing instruments. It has been shown to allow significantly quicker creation of a gastrotomy than the balloon dilation method without increasing the risk of complications.

Though direct incision on the gut wall is a simple method of creating transluminal accesses, concerns regarding peritoneal contamination and the difficulty in closure of the opening have prompted the development of a submucosal tunneling technique<sup>[26-30]</sup>. This technique is the preferred method of transluminal access in mediastinal NOTES and it is also feasible in transgastric procedures<sup>[30]</sup>. In brief, it involves an initial mucosal incision, followed by creation of a submucosal tunnel using either high-pressure carbon dioxide inflation and balloon dilation, or by submucosal dissection, in a manner similar to endoscopic submucosal dissection. The length of the tunnel is reported to be between 5 and 10 cm. At the end of the tunnel, a myotomy is made to gain access into the peritoneal cavity or the mediastinum. This method was shown to be least susceptible to immediate leakage after

closure, with a leak pressure rivaling hand-sewn sutures in study involving 34 *ex vivo* porcine stomachs<sup>[31]</sup>. However, in one study, partial necrosis of the overlying mucosa was observed in up to four out of eight surviving swine (50%), and one swine suffered from severe peritonitis<sup>[27]</sup>. The cause of necrosis might be due to the high-pressure CO<sub>2</sub> bursts used for dissection, leading to impairment of blood supply. Other groups using the same technique without the device did not report such a complication<sup>[28,29]</sup>. Pauli *et al*<sup>[29]</sup> also reported that submucosal tunneling might increase the ease of in-line endoscope positioning to pre-determined abdominal positions.

On the other hand, a number of hollow viscera are available for making accesses to the abdominal cavity. These include the stomach, colon, vagina, and the urinary bladder<sup>[2,20,32,33]</sup>. To avoid the limited maneuverability of a retroflexed endoscope, one will need to consider the access organ and the effect on the in-line position of the endoscope. Theoretically, the transgastric approach should facilitate in-line positioning of the endoscope to pelvic organs, while the transrectal, transvaginal, or transvesical routes provide good forward views of the upper abdominal structures. In an *in vivo* study by Voermans *et al*<sup>[34]</sup> involving 12 swine, transgastric peritoneoscopy was found to be inferior to laparoscopy in detecting simulated peritoneal metastasis, in particular for those located in the liver. In another study, they also found that both transgastric and transcolonic routes provided similar degrees of visualization and access efficacy to the liver and the peritoneal cavity<sup>[35]</sup>. More studies are required to determine the best access route for performing a particular abdominal NOTES procedure, and it is likely that the preference is governed by the nature of the procedures.

## GASTRIC (LUMENAL) CLOSURE AND DEVELOPMENT OF SUTURING AND ANASTOMOTIC DEVICES

The ability to achieve secure luminal closure is pivotal to the success of NOTES. Postoperative leakage is not only associated with morbidity and mortality, but it also bears potential legal and social consequences. Most of the novel designs of NOTES instruments published in the literature have attempted to address this issue. Technological advances in luminal closure can be divided into four groups, namely the clipping, stitching, stapling, and occluding systems (Table 2).

### Clipping systems

**Jumbo endoclips vs over-the-scope clips:** The jumbo endoclip was the earliest described method for luminal closure<sup>[20]</sup>. It is achieved by applying clips to approximate the mucosal edges of an opening<sup>[20,36,37]</sup>. However, the technique can sometimes be difficult, especially if the luminal opening is too large to allow application of the jaws of the clips for mucosal apposition<sup>[38]</sup>. The fact that only the mucosal edges (and perhaps some submucosa

Table 2 Summary of devices for luminal closure in natural orifice transluminal endoscopic surgery

Mechanism of closure	Device name	Outcomes from comparative studies?	Tested in a survival study?
Clipping	Jumbo clips	Yes	Yes
	Over-the-scope clips	Yes	Yes
Stitching	Eagle claw	No	Yes
	T-tags	Yes	Yes
	Loop anchor purse-string	Yes	No
	G-prox needle	Yes	No
	Flexible endostitch	Yes	No
Stapling	SurgASSIST	Yes	No
Occluding	Nitinol cardiac occluder	No	Yes



Figure 2 The Eagle claw.

are recruited in these types of clips renders the security of approximation in large defects very much in doubt<sup>[36]</sup>.

Jumbo endoclips vs over-the-scope clips (OTSC)'s are nitinol clips that return to their original shape after release and allow approximation of large defects similarly to a surgical clamp<sup>[38]</sup>. The additional use of a twin grasper that allows inversion of the seromuscular layers has been shown to enhance approximation of all layers of the bowel wall. Randomized animal studies comparing OTSC's and hand-sewn closures have shown comparable leak pressures<sup>[39-41]</sup>. In another survival study, endoclip closure was found to be associated with significantly higher risk of leakage as compared to OTSC<sup>[42]</sup>.

### Stitching systems

A number of stitching systems have been developed, with none being commercially produced. These include the Eagle claw, T-tags, loop anchor purse-string, G-prox needle, and the Flexible endostitch.

**Eagle claw:** The Eagle claw (Olympus Medical Systems, Tokyo, Japan) was first developed by the Apollo group as an endoscopic suturing device to simulate surgical plication for hemostasis of bleeding peptic ulcers (Figure 2)<sup>[43]</sup>. The device consists of an opposing jaw that opposes tissue on closing and allows passage of a mounted 30 nylon stitch with a detachable needle. A metal pusher then



**Figure 3** Appearance of the T-tags 1 wk after placement for repair of a colonic perforation in an animal model (Courtesy of Professor A Fritscher-Ravens).

tightens the stitch at the two edges of the stomach wall. In our survival study using the swine model, 10 gastrotomies were successfully closed after bilateral fallopian tubal ligation, and none of the animals suffered from suture line leakages upon post-mortem after 2 wk<sup>[44]</sup>. The device is now under development by Apollo Endosurgery and a newer version of the device has been shown to allow both interrupted and running suture placement<sup>[45]</sup>.

**T-tags:** T-tags were first proposed by Fritscher-Ravens *et al.*<sup>[46]</sup> in 2003 and is a device consisting of a series of double tags that are deployed by a transmural needle puncture through the two sides of the gastrotomy. The double tags are then tightened and locked, allowing opposition of the edges of the muscle wall (Figure 3). Other groups have also reported devices with similar design<sup>[27,47,48]</sup>. The device has been shown to produce fluid- and air-tight closures in the porcine model, and full thickness healing was observed. However, a few complications have been reported, including inadvertent injury to surrounding organs during transmural puncture of the needle<sup>[27,47]</sup>.

**Loop anchor purse-string:** This is a variation of the T-tags where the anchors (loop anchors) are modified by adding a small metal wire loop to the crosspiece<sup>[49]</sup>. These anchors are then loaded onto a needle and deployed by using an inner stylet. To achieve gastrotomy closure, a transmural puncture is performed at the edges of the gastrotomy and anchors are deployed sequentially. The stitch is then tightened by pulling on the free ends of the suture and this leads to a purse-string closure of the defect. The device has been shown to achieve significantly higher leak pressures than endoclips in an *ex vivo* model.

**G-Prox needle:** G-prox has an operating mechanism similar to the T-tags. Closure of an enterotomy is achieved by puncturing the two edges of a defect with a 19-gauge needle, after which two pre-loaded expandable baskets connected by a non-absorbable suture are released<sup>[50]</sup>. One end of the suture is then tightened and this causes approximation of the baskets and closure of the defect. The

device has been shown to create closures comparable to hand sewn sutures in an *ex vivo* model.

**Flexible endostitch:** The Flexible endostitch (Covidien, North Haven, USA) was adapted from a rigid laparoscopic version of the device. The jaws of the device holds a double-ended needle attached to a suture thread. The needle is toggled back and forth between the two jaws of the device to create a running suture<sup>[51]</sup>. In the *in vitro* model, it has been shown to produce leak pressures comparable to that of hand sewn sutures.

### Stapling systems

**SurgASSIST:** Long before the advent of NOTES, stapling systems were shown to be reliable methods of creating anastomosis and closure of enterotomy in both open and laparoscopic surgery<sup>[52]</sup>. Flexible stapling systems based on the same technology should theoretically produce a low rate of leakage comparable to their rigid counterparts. SurgASSIST is a mechanically driven flexible linear stapler available from Power Medical Interventions (Langhorne, Pennsylvania, USA), which has been recently acquired by Covidien. The device has an automated firing system that aligns and approximates the staple arms and creates four linear rows of staples with closure of the enterotomy<sup>[53]</sup>. The problem with the device, however, is the difficulty in navigating the two staple jaws into a correct position before closure. Nevertheless, the device has been shown to produce burst pressures comparable to running sutures<sup>[56]</sup>.

### Occluding systems

**Nitinol cardiac occluder:** This occluder was originally designed for closure of atrial septal defects and was proposed to be a possible alternative method for closure of a gastrotomy. Animal survival studies have shown that prolonged closures up to 6 wk were possible with no evidence of leakage<sup>[54]</sup>. Results from comparative studies, however, are still lacking.

## DEVELOPMENT OF A MULTITASKING PLATFORM

It is generally agreed that a multitasking flexible endoscope-based platform designated for NOTES is essential for replication of complex laparoscopic surgical manoeuvres, including dissection and suturing. This has spurred the development of a number of different platforms including the EndoSAMURAI (Olympus Corp, Tokyo, Japan) (Figure 4), the Anubis (Karl Storz, Tuttingen, Germany), the Direct Drive Endoscopic system (DDES) (Boston Scientific, Massachusetts, USA), and the TransPort™ Multi-lumen Operating Platform (USGI medical, California, USA)<sup>[55-57]</sup>. The aim of these platforms is to provide a flexible, yet stable, system through which NOTES procedures can be performed universally through any of the transluminal approaches. Furthermore, these systems should provide a stable image of the operating field comparable to that in laparoscopic surgery



**Figure 4** The EndoSAMURAI (Courtesy of Olympus Co., Tokyo, Japan).

and be independent of the movements of the working arms. More importantly, ergonomic user interfaces are available to control the movements of the arms (some of them capable of five degrees of freedom).

In a bench top simulation setting, both the EndoSAMURAI and the DDES have been shown to significantly enhance performance times and accuracy in complex surgical tasks as compared to using the double-channelled endoscope<sup>[55,56]</sup>. Twelve participants, who included experienced surgeons, medical students, and research assistants, were able to complete a suture using the EndoSAMURAI. The DDES system was also shown to allow performance of complex tasks, such as cutting, grasping, suturing, and knot tying<sup>[57]</sup>. An added advantage of DDES is that it can be operated by a single operator. Performance data of the other multitasking platforms, however, are still lacking and outcomes from human studies are still awaited.

## DEVELOPMENT DEDICATED INSTRUMENTS

### *Flexible instruments and hemostatic appliances*

Another obstacle to performing NOTES in a flexible system is the inferior properties of the endoscopic forceps or coagulation devices currently available when compared to their laparoscopic counterparts. In a recent study comparing the use of monopolar forceps, endoscopic suturing, and argon plasma coagulation in controlling bleeding from a major arterial branch, argon plasma coagulation was shown to be the quickest modality in achieving hemostasis<sup>[58]</sup>. In another study, the use of novel flexible bipolar forceps was shown to be comparable to laparoscopic bipolar forceps in stopping bleeding from blood vessels ranging from 1.5 to 6 mm in diameter. Delayed bleeding was observed in 3% of the blood vessels when blood pressure was raised to more than 200 mmHg for 10 min<sup>[59]</sup>. The development of other flexible instruments has also been announced but their performance data are still pending<sup>[60]</sup>.

## HUMAN NOTES PROCEDURES

Despite the tremendous amounts of research being directed towards NOTES, reports of human NOTES procedures are still limited. The majority of the publications

were case series or single case reports, and only one study was comparative (Table 2)<sup>[2-16]</sup>. The most reported human NOTES procedure was a cholecystectomy and these procedures were performed *via* the transvaginal or transgastric routes<sup>[2,3,10-13]</sup>. NOTES peritoneoscopy, sleeve gastrectomy, sigmoidectomy, and nephrectomy have also been reported<sup>[4-9,14-16]</sup>. The NOTES appendectomy performed in India have been widely cited as a personal communications, but published data is still being awaited.

In fact, most NOTES cholecystectomies reported to date are hybrid procedures<sup>[2,3,5,10-13]</sup>. A 2 to 5 mm transumbilical port was first inserted for insufflation of pneumoperitoneum and also to allow for monitoring of the procedure. Most studies achieved transluminal access *via* the transvaginal route but the transgastric approach has also been described. In transvaginal cholecystectomy, a posterior colpotomy was made under direct laparoscopic view through the umbilical port and one to two trocars were inserted<sup>[10]</sup>. Both a flexible and an ultra-long rigid system have been used to perform the procedure. Retraction of the gallbladder was achieved by the umbilical port or additional transvaginal ports. In cases where a flexible endoscope was used, dissection was performed using instruments inserted through channels of the endoscope and clipping of the cystic artery and duct were done with either endoscopic hemoclips or surgical clips through the transumbilical or transvaginal trocars. In cases where a rigid system was used, the procedure was performed in a manner similar to traditional laparoscopic cholecystectomy, using ultra-long rigid instruments introduced through the transvaginal trocars.

In the human series describing NOTES cholecystectomy (Table 1), three out of 86 operations were unsuccessful and none required conversion. These three patients suffered from severe pelvic adhesions that prevented transvaginal insertion of trocars. The mean time to completion of the operation ranged from 51 to 135 min and no major complications were reported. In the largest series including 68 patients, the patients were also interviewed at 3 to 10 mo after surgery and none of them had abdominal or gynecological complaints in relation to sexual intercourse<sup>[9]</sup>.

In the only human NOTES comparative study, transgastric peritoneoscopy was compared to diagnostic laparoscopy in evaluating patients with a pancreatic mass. Transgastric peritoneoscopy confirmed the decision to proceed to open laparotomy in nine out of ten patients, and the procedure was found to be safe and feasible. However, the authors also commented that the accesses to the right lobe of the liver and right upper quadrant structures were inadequate endoscopically and that attempted biopsies were unsuccessful due to inability to reach these areas<sup>[5]</sup>.

On the other hand, there have also been case reports describing transvaginal nephrectomy, sleeve gastrectomy, and sigmoidectomy<sup>[6,7,9,15,16]</sup>. All these procedures were hybrid procedures where a transumbilical port was inserted for monitoring and retraction of the tissues, while the transvaginal ports were used for dissection and retrieval of

the specimen. All procedures were successfully performed and none reported major complications.

## COMMENTS

The NOTES white paper in 2005 identified a number of fundamental obstacles to implementation of NOTES in humans<sup>[1]</sup>. Since then, these issues have become key areas of rigorous research in the laboratory setting and many findings have been published in the literature. Of interest is that, with the exception of case series and reports of human NOTES described in this paper, all of the studies performed so far were in animals. It is obvious that the intrinsic differences in physiology and anatomy between animals and humans do have significant impacts on the outcomes of the procedures, and whether results obtained in animals can be replicated in humans remains uncertain. More importantly, implementation of NOTES in human is still severely impaired by the availability of reliable devices specific for the procedure. The majority of devices that were described in this review remain as prototypes that are available to only a few exclusive centers. This limits the ability of researchers to compare different devices and procedures, let alone document the safety profiles and efficacy over a large study population.

In terms of the methods of gaining transluminal accesses, several problems remain to be solved. Firstly, the optimum method of creating the transluminal enterotomy is still uncertain. To some extent, the type of procedure being performed governs the methods of creating the opening. The submucosal tunneling method might be more appropriate when access to a particular organ is required. Likewise, the optimal access organ that provides the best in-line positioning when performing NOTES procedures on a specific region within the abdominal cavity will need to be determined. These issues remain to be resolved in future studies.

The NOTES white paper also states that a closure device that allows 100% reliability is a must before NOTES could be more widely implemented in humans. Along this line, many novel closure devices have been developed over the years. However, none of the reports have included a sufficiently large sample size to determine the exact risk of leakage. Direct head-to-head comparison of these devices has only been performed in one *in vitro* study, and there is a paucity of literature concerning the difference in *in vivo* efficacy of these devices<sup>[52]</sup>. Without these data, it is unlikely that any of the manufacturers will agree to undergo clinical human trials.

Besides closure devices, another area with exciting development is the research on flexible endoscope based multitasking platforms and instruments. The EndoSAMURAI, DDES, and the TransPort Multi-lumen Operating Platform™ were developed with an aim to perform complex transluminal procedures<sup>[55-57]</sup>. At present, most of these devices are still cumbersome to use and have been tested only in an *in vitro* setting. Size, ease of introduction, maneuverability *in vivo*, and lack of tactile feedback are some of the problems of the current platforms, which

need to be addressed before they can be put into use in human subjects. It is also not certain how well they actually perform in a surgical operation, when grasping, dissecting, ligating, and suturing movements are performed in conjunction.

For the above reasons, the emergences of human NOTES procedures have largely been based on rigid platforms. This has been made possible by the adoption of ultra-long laparoscopic instruments introduced transvaginally, which allows replication of the steps of a laparoscopic surgical procedure. This may well be an intermediate form of NOTES before more reliable and steady platforms become available. Thus far, the outcomes of these NOTES procedures using laparoscopic instruments have been encouraging, and results from comparative studies are eagerly awaited to determine whether NOTES can truly offer earlier recovery and improve cosmesis.

## CONCLUSION

Significant advances have been made in recent years in addressing the key obstacles to safe performance and introduction of human NOTES. However, most studies to date are still largely experimental, and whether these performance data can be repeated in humans remains uncertain. On the other hand, reports of human NOTES procedures are beginning to emerge. These studies have demonstrated the feasibility of performing human NOTES using existing technology. Dedicated devices are still lacking to allow for pure NOTES. Whether NOTES can deliver the postulated benefits of earlier recovery and improved cosmesis has yet to be confirmed.

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