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Experimental foundation for natural orifice transluminal endoscopic surgery and hybrid natural orifice transluminal endoscopic surgery

Estevao Lima*†, Carla Rolanda*‡, Riccardo Autorino§ and Jorge Correia-Pinto*¶

**Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Braga, Portugal; †Department of Urology, Santo António General Hospital, Porto, Portugal; ‡Departments of Gastroenterology, São Marcos Hospital, Braga, Portugal; §Urology Clinic, Second University of Naples, Italy; ¶Department of Pediatric Surgery, Hospital São Joao, Porto, Portugal*

Natural orifice transluminal endoscopic surgery (NOTES) is one of the most exciting concepts that has emerged recently in the surgical field. All accesses to the abdominal cavity in the porcine model using natural orifices, e.g. transgastric, transvesical, transcolonic and transvaginal, have been described and explored. The experimental feasibility of all procedures by NOTES was successfully demonstrated in the porcine model using different types of natural orifices. However, few translations to the human have been made. NOTES is in a developmental stage and much work is still needed to refine techniques, verify safety and document efficacy. This paper is an update on the experimental foundation for NOTES and hybrid NOTES and examines the opportunities presented by this new surgical vision.

KEYWORDS

endoscopy, NOTES, transgastric surgery, transvesical surgery

INTRODUCTION

Over the last few decades, the major drive in surgery has been the development and application of minimally invasive approaches to traditional operations. This philosophy has crossed all surgical specialties, and progressively in urology since the early 1990s the laparoscopic technique has been adopted for the majority of urological procedures [1]. Moreover, urologists have also been the pioneers in the implementation of novel minimally invasive techniques such as percutaneous surgery, robotics and therapeutic urinary endoscopy [2]. Nowadays, minimally invasive techniques are the method of choice for treating the most common urological conditions with the exception of trauma and renal transplantation (Table 1). It has become apparent that minimally invasive surgery is associated with faster recovery and earlier return to full activity. In addition, surgeons would agree that the small incisions of laparoscopic surgery are associated with less pain and a better cosmetic outcome than open laparotomy [3].

Simultaneously, other specialties such as gastroenterology have changed progressively and dramatically over the last few decades [4]. Initially, endoscopic evaluation of the gastrointestinal tract was a diagnostic procedure with very limited therapy. Subsequently, endoscopic biopsy, haemorrhage control and the snaring of polyps was a marked advance over previous methods of management, which often involved open exploration. Recently endoscopists have expanded the indications for endoscopic therapeutic manipulation and there seems to be a convergence of the once separate ways of gastrointestinal endoscopy and surgery. However, the potential of flexible endoscopy for performing therapeutic procedures beyond the wall of the gastrointestinal tract was recognized in 1980 when the first percutaneous endoscopic gastrotomy was described by Gauderer *et al.* [5]. More recently, Kozarek *et al.* [6] showed that even pancreatic pseudocysts can be managed transgastrically. Envisioning evolution Reddy and Rao from India performed a very controversial procedure: human transgastric appendicectomy [7]. Recognizing the potential benefits of this procedure, in 2004 Kalloo *et al.* [8] pursued the idea by testing in pigs the feasibility and limitations of abdominal surgery without scars through a transgastric port. This was the birth of natural orifice transluminal endoscopic surgery (NOTES). The approach was thought to have several advantages since it would avoid abdominal incisions and all the consequences of them, such as incisional hernias and infections of surgical wounds. Moreover, it has the theoretical potential to reduce postoperative pain and recovery time compared with laparoscopy [7]. This makes sense because the factors that cause visceral pain are different from those that cause somatic pain. It has been known for several years that cutting the gut and viscera rarely elicit pain.

With the visceral wall no longer a barrier to endoscopic intervention, various authors performed more complex abdominal procedures in animal models ranging from tubal ligation to splenectomy [9–21]. Believing in the potential benefits of the natural orifices approach for abdominal surgery, Lima *et al.* [22] hypothesized that other ports would be advantageous. In this sequence, they assessed the feasibility and safety of creating a transvesical port for the abdominal cavity. As occurred with the transgastric port, the transvesical approach also broke a classical sanctuary of urology: the wall of the urinary tract. In fact, perforations of the bladder wall were always feared as a potential complication of urological procedures.

TABLE 1 Current urological procedures

Open procedure	Percutaneous	Endoscopy	Laparoscopy
Adrenalectomy			×
Simple nephrectomy			×
Radical nephrectomy (T1-2)			×
Nephroureterectomy			×
Treatment of renal cysts	×		×
Treatment of renal lithiasis	×	×	
Endopyelotomy and ureteropyeloplasty	×	×	×
Treatment of ureteric lithiasis		×	
Treatment of bladder lithiasis	×	×	
Prostatic enucleation or resection		×	

×, *the gold standard.*

TABLE 2 Potential challenges to clinical application of transgastric port

Peritoneal access
Gastric closure
Prevention of infection
Suturing and anastomosing devices
Developing a multi-tasking platform
Effective organ retraction, secure grasping, good triangulation
Management of complications

In the remaining text, we review the experimental foundations of NOTES and hybrid NOTES.

THE FIRST WORKING GROUPS ON NOTES

With these first descriptions of NOTES procedures, there was a major debate about the potential benefits from transgastric access and the challenges that it was causing regarding the limitations that were being identified by the few groups that were testing the transgastric port experimentally. There was a consensus that transgastric access was not totally sterile and the difficulties in its endoscopic closure could cause serious complications in abdominal surgery. Despite aggressive criticism from the most conservative surgeons and endoscopists, the possibility of performing scarless surgery nursed an increasing number of dreamers and believers in NOTES. Thus, in 2006, a joint effort from key persons from the American Society for Gastrointestinal Endoscopy (ASGE) and the Society of American Gastrointestinal Endoscopic Surgeons (SAGES) organized the Natural Orifice Surgery Consortium for Assessment and Research [7]. This organization collected the preliminary data and summarized in a White Paper the most important limitations and some potential strategies to overcome them. European researchers also formed the European Association of Transluminal Surgery (www.eats.fr) and the EURO-NOTES Foundation (www.euro-notes.eu) to ease cooperation between the European Association for Endoscopic Surgery and the European Society of Gastrointestinal Endoscopy, which focuses on NOTES-related activities. More recently, it created the Urology Working Group on NOTES. The initial objectives of this group were (i) to increase awareness of NOTES in urology; (ii) to provide an outlet to share discoveries related to urological NOTES; (iii) to guide scientific evaluation and implementation of urological NOTES; (iv) to facilitate learning opportunities with urological NOTES; (v) to define nomenclature of urological NOTES. The vision of this working group is to safely and systematically implement NOTES in urology [23].

THE FIRST EXPERIMENTAL STUDIES IN NOTES AND HYBRID NOTES

Natural orifice surgery began in 1901 with Dimitri Ott [24], working in Petrograd, who described the technique as 'ventroscopy'. In this procedure he used a speculum that was introduced through an incision in the posterior vaginal fornix. This transvaginal approach was forgotten until 1928 when Decker [25] performed some culdoscopies. In 2002, Gettman *et al.* [26] described the first experimental application of natural orifice surgery when transvaginal nephrectomy was performed in the porcine model. This procedure indeed pre-dated the acronym NOTES. He performed nephrectomy in five female pigs using a single 5-mm abdominal trocar; however, limitations related to the porcine model and instrumentation made the procedure cumbersome. Kalloo *et al.* [8] reported the first natural orifice endoscopic surgery using a transgastric approach in a porcine model in which they orally introduced a flexible endoscope into the peritoneal cavity to perform peritoneoscopy and liver biopsies. At the end of the procedure, researchers closed the gastric wall with endoscopic clips. In five experiments, all pigs recovered and gained weight.

Several studies [9–20] have since used the transgastric port for intraperitoneal abdominal procedures, such as fallopian tube ligation, cholecystectomy, gastrojejunostomy, lymphadenectomy, oophorectomy, partial hysterectomy, splenectomy, diaphragmatic pacing, appendicectomy, hernia repair and pyloroplasty. Following the initial enthusiasm, however, abdominal procedures through isolated transgastric routes showed limitations that jeopardized application in humans. Potential barriers to clinical practice included safe access to the peritoneal cavity; gastric closure; infection prevention; spatial orientation; stable multi-tasking platform to obtain adequate anatomy exposure, organ retraction, secure grasping and triangulation; difficulty in controlling the pneumoperitoneum; and management of iatrogenic intraperitoneal complications (Table 2) [7]. These limitations, which led to surgeons losing some important principles from classical and laparoscopic surgery during transgastric procedures, are primarily related to the nature of the gastroscope instruments (flexible and parallel), such as (i) absence of triangulation, (ii) poor retraction capability and (iii) the necessity to work frequently in retroflexion with an inverted image.

Lima *et al.* [22] hypothesized that the development of a lower abdominal port for introduction of rigid instruments would be a simple and easy way to overcome most of the limitations of the isolated transgastric port.

Using current urological instruments, this group planned an atraumatic method to create a transvesical port. In a preliminary experimental study, they demonstrated in a porcine model that the transvesical endoscopic approach to the peritoneal cavity was feasible and easy to create without any further complications even when the vesicotomy was left open with just a bladder catheter.

The transvesical port has properties that make it an excellent access to the abdominal cavity. In fact, the access is naturally sterile, and anatomically is the most anterior lower abdominal port providing instrument access to the peritoneal cavity above the bowel loops. Moreover, it allows the introduction of rigid instruments into the peritoneal cavity enhancing the possibility of retracting structures easily. The only disadvantage is that the diameter of the urethra limits specimen retrieval and the size of the instruments used in this approach.

Given the good results from the first study using the transvesical route, Lima *et al.* [27] tested the possibility of reaching the thoracic cavity, after passing the diaphragm. In this study, although the researchers were able to perform only limited thoracoscopy and lung biopsies, the intervention field of NOTES was definitively extended from the peritoneal to the thoracic cavity.

Cholecystectomy has been considered the most challenging for the isolated transgastric approach. Using two endoscopes or a single endoscope conjugated with a transabdominal trocar, Park *et al.* [10] and Swanstrom *et al.* [28] experienced significant difficulties performing cholecystectomy using shape-lock technology. Confirming the initial hypothesis that the transvesical approach would overcome some limitations of isolated transgastric access, Rolanda *et al.* [29] demonstrated that adding the transvesical to the transgastric port provided the surgical team with a better surgical triangulation and effective retraction. With this strategy the group reported for the first time third-generation cholecystectomy by pure NOTES with combined accesses (transgastric and transvesical ports), launching the concept of combined or multiple ports for NOTES. More recently, Lima *et al.* [30] used the same combined approach to perform nephrectomy.

Subsequently, another group [31,32] from Harvard University developed the transcolonic access concurrently with the transvesical approach. This study confirmed the benefits of a lower abdominal access, namely the possibility of introducing rigid instruments and direct imaging from the upper abdominal organs, which motivated them to perform transcolonic cholecystectomy. However, the transcolonic port retains many of the limitations previously described for the transgastric port, because it is not sterile and requires a reliable and effective closure device that is not available even now.

Given the ongoing difficulties in finding safe devices for endoscopic closure, several investigators tried to re-discover the transvaginal access (posterior colpotomy), which had been used for many years by gynaecologists to perform pelvic interventions. This access provided the same benefits as the transvesical and transcolonic accesses and was safer because it is easily closed without an endoscopic device by surgical stitches from outside. In fact, the transvaginal port allows introduction of rigid instruments and organ retrieval even of large dimensions [26]. These characteristics gave confidence to Zorron *et al.* [33] from Rio de Janeiro in Brazil, Bessler *et al.* [34] from New York in the USA and the Marescaux group [35] from IRCAD, Strasbourg, in France in 2007 to perform the first hybrid NOTES cholecystectomy in humans using combinations of transvaginal and transabdominal trocars. This procedure readily became popular and widespread. However, the approach still has a serious constraint as it is only available for women.

EXPERIMENTAL TECHNIQUES FOR PERITONEAL ACCESS USING NATURAL ORIFICES

As in laparoscopy there is discussion about the way to choose the first trocar to start the pneumoperitoneum and to monitor the placement of the other ports; accessing the peritoneal cavity through a natural orifice always risks damaging the adjacent organs during creation of the hole in the visceral wall. Accessing the peritoneal cavity in a blind way through the transgastric port can damage adjacent organs, as reported by many authors. Interestingly, the technique to establish the transvesical port was described using neither cutting instruments nor cautery, which makes the transvesical port a safe route to start access to the peritoneal cavity [36]. Another established safe approach to the peritoneal cavity is the transvaginal port. Using this route we can have vision also [33–35]. Thus, the transvaginal and transvesical ports can be particularly useful in procedures involving multiple natural orifices, since the transvaginal or transvesical image can easily monitor the transgastric creation [24,29].

The placement of the transvesical port is based on the Seldinger principle. Currently, Lima *et al.* [36] use a ureteroscope introduced through the urethra into the bladder with pneumo-distension; the bladder is emptied of urine and distended with CO_2. The vesicotomy site is carefully selected on the bladder dome. A mucosal incision is made with scissors introduced through the working channel of the ureteroscope. Subsequently, a 5-F open-ended ureteric catheter is pushed forward through the incision into the peritoneal cavity. A 0.035-inch flexible-tip guidewire is then inserted into the peritoneal cavity through the lumen of the ureteric catheter. Guided by the flexible-tip guidewire, the vesical hole is enlarged with a dilator of a ureteroscope sheath enveloped by a flexible 5.5-mm overtube. A ureteroscope is introduced into the peritoneal cavity through the overtube and allows the creation of a pressure-controlled CO_2 pneumoperitoneum. More recently Gettman and Blute [37] used the same technical mode in humans with a few modifications such as a ureteric balloon instead of a ureteric catheter.

Several variants have already been described for establishing the transgastric port [8–21]. The classical technique begins with introduction of the gastroscope in the stomach and the placement of an overtube. Then the stomach is lavaged and disinfected with an antibiotic for 10 min. Subsequently, various techniques for gastrotomy have been reported, with the most common location for the incision being the anterior gastric wall. A needle-knife incision can be made to puncture the wall and then extend the gastrotomy, or for positioning a guidewire in the peritoneal cavity. Over the guidewire the puncture dilatation is performed with an 18-mm through-the-scope balloon. Then, the gastroscope is pushed forward and passed into the peritoneal cavity. A percutaneous endoscopic gastrotomy has been described [38] to help prevent damage to adjacent structures. By contrast, Rolanda *et al.* [29]

prefer to establish it under outside view in order to avoid damage of the gastric wall vessels or adjacent organs. This research group thinks that blind gastrotomy should not be done, at least with current methods. Thus, all the procedures can be monitored by a scope positioned through a lower abdominal access or transabdominally. Recently, with the objective of minimizing peritoneal soiling and simplifying the gastric closure, Sumiyama *et al.* [39] reported submucosal endoscopy with a mucosal flap safety valve technique as a safer methodology to access the peritoneal cavity for transgastric procedures. This method requires the submucosa to be separated with a high-pressure CO_2 injection followed by balloon dissection to create a working space. The submucosal space can provide a protective offset entry to the peritoneal cavity, which may minimize peritoneal soiling by using the overlying mucosa as a sealant flap. The submucosal endoscopy with mucosal flap technique allows safe trans-oesophageal access into the mediastinum and cholecystectomy by the transgastric approach.

The transcolonic port is also being developed [31,32]. A sterile dual channel endoscope is introduced through the anus and advanced 15–20 cm from the anal verge. A needle knife is used to make a sub-centimetre linear incision. Once the incision is complete, the needle knife is retracted; the catheter is advanced through the incision into the peritoneum and the endoscope is then advanced through the colonic wall into the peritoneal cavity.

The transvaginal port was described a long time ago and has already been used for several intra-abdominal procedures by gynaecologists [25]. Recently, there has been a resurgence of enthusiasm for the transvaginal port for upper abdominal procedures since it does not have the risks of the transgastric port [33–35]. The method is easy. Briefly, the peritoneal cavity is entered through an incision in the posterior vaginal cul-de-sac.

COMPARISON OF DIFFERENT PORTS THROUGH NATURAL ORIFICES TO THE PERITONEAL CAVITY

From the description of the transgastric port many limitations are evident; the most important is that the per-oral route is not sterile and certainly bacteria will gain access to the peritoneal cavity. Although a temporary open gastrotomy is probably not harmful, peritoneal spillage from a leaking closure may be devastating. Therefore, substantial effort should be devoted to assuring a reliable method of viscerotomy closure if this port is to be used in humans. The second limitation is a result of the long distance from the mouth to the stomach that requires the use of flexible devices and instruments. Most currently available equipment is inadequate for performing retraction and meticulous dissection. Thus, routine human application of the transgastric port should probably not be performed until technical advances materialize.

From the description of lower abdominal accesses and the first animal experiences several conclusions can be drawn; for example, the lower abdominal ports are better for upper abdominal procedures and useful as accessory ports for transgastric access (Table 3). Although these accesses share the possibility of introducing rigid instruments into the abdomen, the transvesical port appears to give the most anterior positioning in the sagittal plane and allows the possibility of working above bowel loops instead of through them as with the transvaginal or transcolonic port. The transcolonic port allows good access to the peritoneal cavity mainly for the upper abdomen, but the risk of peritoneal infection is high and refinements in colonic preparation, luminal sterilization and closure techniques will be required before translation to humans. Thus, the current status of NOTES development seems to select the transvaginal port as the most reliable for human application at this moment. Transvaginal access is the unique natural orifice port that has a reliable method for closure. This is the rationale for the use of this approach by many surgeons. However, it has a serious limitation since it is available only for women and raises serious psychological concerns that we are still far from fully understanding.

TABLE 3 Clinical comparison of gastric and lower abdominal accesses

	Stomach	Bladder	Vagina	Colon
Rigid instruments	No	Yes	Yes	Yes
Available in both genders	Yes	Yes	No	Yes
Sterility	No	Yes	No	No
Size	Wide	Narrow	Wide	Wide
Closure	Under study	Under study	Yes	Under study
Specimen retrieval	Yes	No	Yes	Yes

THE FIRST NOTES EXPERIMENTAL PROCEDURES IN UROLOGY

The first attempt at NOTES was made by Gettman *et al.* [26] who performed a complete transvaginal laparoscopic dissection and nephrectomy in a porcine model. With the NOTES acronym already established and with the intention of linking urology to NOTES, Lima *et al.* [22] described the transvesical approach to the peritoneal and thoracic cavity. After these initial descriptions, in a single human case [37], transvesical peritoneoscopy was used to evaluate suprapubic tube placement in conjunction with robotic prostatectomy. Recently, Clayman *et al.* [40] revisited the transvaginal access idea and carried out a porcine nephrectomy with a single 12-mm trocar placed in the midline and the transvaginal introduction of a TransPort Multi-lumen Operating Platform (USGI Medical, San Clemente, CA, USA). This flexible device has four working channels and can be locked into position, creating a rigid multi-tasking platform that enables two-handed tissue manipulation. The same research group [41] also recently reported a transvaginal hybrid NOTES nephrectomy using the da Vinci S robot (Intuitive Surgical, Sunnyvale, CA, USA). Stretching the limits, Lima *et al.* [30] demonstrated the feasibility of NOTES nephrectomy. In a non-survival study, combined transgastric and transvesical approaches were established in six female pigs. Under ureteroscope visualization through a 5-mm transvesical port, researchers controlled the orally introduced flexible gastroscope by a gastrotomy into the

peritoneal cavity. Right or left nephrectomy was carried out using instruments introduced by devices that worked in the renal hilum, alternating intervention on dissection or retraction procedures. In all animals, both kidneys were visualized, and the renal vessels and ureter were reasonably individualized and ligated separately with ultrasonic scissors introduced through the transvesical port. More recently, another combined NOTES nephrectomy technique was described by Isariyawongse *et al.* [42] using combined transgastric and transvaginal access. Transgastric endoscopic visualization was first placed in the peritoneal cavity and then guided the introduction of a second transvaginal endoscope. The retroflexed transgastric endoscope provided triangulated visualization as standard endoscopic instruments provided retraction, which allowed dissection of the kidney with standard laparoscopic instruments through a modified transvaginal trocar device. The renal hilum, artery, vein and ureter were dissected and divided with a transvaginal laparoscopic stapler. Using robotics and magnetically anchored instrumentation, Zeltser *et al.* [43] performed a single trocar laparoscopic nephrectomy in two pigs, trying to overcome the current limitations for scarless nephrectomy. Nephrectomy will most probably be one of the latest renal procedures potentially performed by pure NOTES in the future. However, using two 5-mm abdominal trocars and vaginal placement of an endoscope, Branco *et al.* [44] described hybrid NOTES transvaginal nephrectomy to remove a non-functioning right kidney in a human. The total procedure time was 170 min and no complications occurred. This was the first published clinical application of the hybrid concept in the urological field.

Transvesical access has faced some reluctance from the medical community since we did not describe a way to close it in our first description. Thus, Lima *et al.* [45] tested the usefulness of T-fasteners with a locking cinch system in bladder closure. The research group demonstrated the feasibility and the safety of endoscopic closure of vesical perforations with an endoscopic suturing kit (T-fasteners with a locking cinch) in a survival porcine model. These findings provide immediate support for clinical application of this method to close bladder perforations both in management bladder rupture and in transvesical ports in NOTES procedures.

CONCLUSIONS

NOTES is a revolutionary peritoneal cavity intervention that is a natural convergence of intraluminal (endoscopy) and extraluminal (laparoscopy) endoscopic techniques: a third-generation surgery after open surgery (first generation) and laparoscopy (second generation) that requires new equipment, special training and often interdisciplinary collaboration. Most criticism against NOTES echoes what was said against those who were pioneering laparoscopic surgery in the late 1980s. Laparoscopic surgery has now become a gold standard in the treatment of many abdominal diseases. We should have learned the lesson and look at new upcoming techniques with a good attitude.

Currently available instruments are designed to function inside the urinary and gastrointestinal tract and have some limitations when used inside the peritoneal cavity. It is very difficult to predict the future. Certainly the birth of NOTES is pushing research and surgeons to design a new generation of instruments and equipment. As technology develops, NOTES may be able to take off.

CONFLICT OF INTEREST

None declared.

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Correspondence: Estevao Lima, Escola de Ciências da Saúde, Universidade do Minho, Campus de Gualtar, 4709-057 Braga, Portugal.
e-mail: estevaolima@ecsaude.uminho.pt

Abbreviation: **NOTES**, natural orifice transluminal endoscopic surgery.