Universidade do Minho
Escola de Ciências da Saúde

Carla Rolanda Rocha Gonçalves

N.O.T.E.S
PERORAL TRANSLUMINAL ENDOSCOPIC SURGERY

Agosto de 2009

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PERORAL TRANSLUMINAL ENDOSCOPIC SURGERY

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"Imagination is more important than knowledge"

Albert Einstein (1879-1955)

Aos meus pais, Joaquim e Piedade

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Neste momento é inevitável um olhar retrospectivo e uma reflexão. Sinto-me privilegiada. Por isso, esta tese não cristaliza apenas os resultados científicos, mas também os sentimentos e as vivências deste período, afinal é disso que tratam os grandes avanços - sonho, crença, colaboração e partilha. Para o laboratório trouxe a inquietação e o gosto pela minha especialidade, para a prática clínica levei novas ideias, capacidades técnicas acrescidas e entusiasmo, quanto aos que me abordam e escutam a esses tenho muito mais para transmitir. Acabei naturalmente por integrar o conceito de médico - investigador - professor e por acreditar nele. O privilégio foi concretizá-lo neste projecto, nestas circunstâncias e com estas pessoas. As pessoas, que neste vaivém de actividades directa ou indirectamente contribuíram para este trabalho, para o meu bem-estar e para a materialização desta tese. É a elas que expresso a minha sincera gratidão:

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resumo

O conceito de NOTES (Natural Orifice Transluminal Endoscopic Surgery) emergiu como uma natural consequência da evolução na endoscopia digestiva alta. Na verdade, a abordagem per-oral proporciona acesso a ambas as cavidades corporais, o abdómen e o tórax, através dos acessos transgástrico e transesofágico, respectivamente. O potencial de se transformar a cirurgia numa intervenção menos dolorosa e sem cicatrizes impulsionou o interesse por estas duas abordagens, porém há três problemas que continuam a limitar a sua translação para Humanos: i) criação segura da enterotomia, ii) manipulação adequada dos tecidos e iii) encerramento eficaz da enterotomia. Os objectivos desta tese de doutoramento foram delineados no sentido de trabalhar e ultrapassar algumas dessas limitações. Assim, elaboraram-se quatro protocolos experimentais em modelo suíno: nos protocolos 1 e 2, explorou-se a combinação da porta transgástrica com outro acesso natural diametralmente oposto (transvesical) que se mostrou vantajosa na manipulação dos tecidos durante procedimentos abdominais complexos (colecistectomia e nefrectomia); no Protocolo 3, avaliou-se o encerramento da gastrotomia *in-vivo* com o sistema OTSC (over-the-scope-clips) após varicocelectomia transgástrica; no Protocolo 4, testou-se a exequibilidade de uma esofagectomia segmentar seguida de anastomose esófago-esofágica de camada única, termino-terminal, por via transesofágica com assistência de um único trocar transtorácico. Os procedimentos de colecistectomia, nefrectomia e varicocelectomia foram efectuados com êxito por NOTES puro, recorrendo à combinação das vias transgástrica e transvesical ou, no último caso, à via transgástrica isolada. O sistema OTSC demonstrou ser um método fiável para o encerramento de gastrotomias seleccionadas, enquanto a nossa estratégia híbrida para controlar de forma segura a criação e o encerramento do acesso transesofágico se revelou bem sucedido. Desta feita, os procedimentos acima apresentam-se como possíveis alvos de intervenção NOTES. Tendo em conta os resultados experimentais expostos nesta tese e o desenvolvimento tecnológico em curso, é razoável esperar para breve a disseminação do NOTES em Humanos, com vantagens para os pacientes.

abstract

Natural Orifice Transluminal Endoscopic Surgery (NOTES) concept emerged as an evolution of upper gastrointestinal endoscopy. In fact, the peroral approach provides access to both corporal cavities the abdomen and the thorax, trough a transgastric and a transesophageal access, respectively. The potential for scarless and painless surgery push forward the interest on these two approaches, although three main limitations remain struggling Humans' translation: i) enterotomy safe creation, ii) reliability on tissues manipulation, and iii) enterotomy closure. The aims of this PhD thesis were delineated to deal and overcome some of these problems. Thus, we carried out four experimental protocols in the porcine model: in protocols 1 and 2, we explored the advantageous combination of transgastric with a diametrically opposed natural orifice (transvesical) for tissue manipulation and dissection in abdominal complex procedures (cholecystectomy and nephrectomy); in protocol 3, we assessed *in-vivo*, the gastrotomy closure with the over-the-scope-clips (OTSC) system after transgastric varicocelectomy; in protocol 4, we tested the feasibility to perform a peroral esophageal segmentectomy with a subsequent complete, single-layer and end-to-end esophago-esophageal anastomosis with a single transthoracic trocar assistance. Cholecystectomy and nephrectomy or varicocelectomy were successfully performed by pure NOTES, using either a transgastric and transvesical combined approach or just an isolated transgastric access, respectively. The OTSC system confirmed to be a reliable method for selected gastrotomy closure, whereas our hybrid strategy for monitoring creation and closure of the transesophageal access was also successful. By this way, the previous described procedures were launched as possible targets for NOTES. Taking all together, the results of the experiments exposed in this thesis and the current developments in instruments and equipment, it sounds reasonably to believe that the momentum of Human NOTES is arriving soon with advantages for patients.

abbreviations

CCD - Charged-couple device chip
CO_2 - Carbon dioxide
EMR - Endoscopic mucosal resection
ERCP - Endoscopic retrograde cholangiopancreatography
ESD - Endoscopic submucosal dissection
EUS - Endoscopic ultrasound
GI - Gastrointestinal
GIST - Gastrointestinal stromal tumor
MIS - Minimally invasive surgery
NOTES - Natural orifice transluminal endoscopic surgery
OTSC - Over-the-scope-clips
PEG - Percutaneous endoscopic gastrostomy

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PART I
introduction

Chapter 1. Evolution of Endoscopy Towards NOTES

1.1 – GASTOINTESTINAL ENDOSCOPY

The desire of physicians to inspect the hollow organs long preceded their ability to do so. We could retrocede to Hippocrates in Greece (460-375 B.C.) and his rectal speculum, pursuing along the centuries all the futile attempts to overcome this challenge, but the term endoscopy and the real intent to produce usable endoscopes started in the nineteenth century with Desormeaux, a French surgeon (reviewed by Rosin 1993).

At that time the greater barrier was the lack of adequate illumination, and a proposed source of light was the gasogen (alcohol and turpentine) lamp. Desormeaux used it in 1853 for a cystoscope, and Kussmaul in 1868 for a rigid gastroscope that he tested in a sword swallower - the first gastroscopy ever performed (reviewed by Walk 1996). Edison's invention in 1879 brought the end of the dark ages of endoscopy. Incandescent lamps had been miniaturized, and Nitze together with Leiter, produced the first cystoscope in 1886. Shortly thereafter, Mikulicz and Leiter developed a successful rigid open-tube esophagoscope, which was later adapted and used by ear, nose, throat and thoracic surgeons, with minor modifications until recent time. They also developed a gastroscope but it had a high risk of organ rupture and only the esophagoscope proved to be acceptable. The esophagoscopy and bronchoscopy remained the field of otorhinolaryngologists for decades (reviewed by Haubrich 1987).

In 1932, after 4 years of collaboration with Wolf, Schindler presented the final version of his semiflexible gastroscope using principles of optical physics, and by the end of 1933 Schindler's expertise in gastroscopy was widely recognized (Schindler 1950). During the Nazi regime in Germany, Schindler immigrated into Chicago and there started the Gastroscopic Club, the forerunner of the American Society for Gastrointestinal Endoscopy (ASGE) (reviewed by Gerstner 1991). Besides some improvements such as addition of a biopsy channel, Schindler's gastroscope had many disadvantages: the hyperextension of the neck with major discomfort for the patient, the impossibility of esophagus and duodenum visualization, and the problem of blind areas in the stomach (parts of the antrum and fundus) making the procedure incomplete (reviewed by Edmonson 1991). In 1956, Hirschowitz presented and swallowed himself the prototype of the first gastroduodenal fiberscope, a revolutionary totally flexible gastroscope, but still with a side-viewing (Hirschowitz at al. 1958). In the mid-1960s progressively appeared the forward-viewing endoscopes with lens washing, cold light, insufflation capability, channels for aspiration and biopsy, and the new era for upper and lower endoscopy began (reviewed by Haubrich 1997). In the meantime, Itaru Oi astonished the audience of the World Congress of Gastroenterology in 1970 with the endoscopic retrograde cholangiopancreatography (ERCP), bringing to light the obscure pancreas and the biliary tree (Oi et al. 1970).

In 1983 the image of the coherent fiber bundle was replaced by electronic video technology using a charged-couple device (CCD) chip, and the first workable video endoscope was presented (Classen et al. 1984). In 1994 the use of these systems becomes generalized, it was a revolution for teaching in endoscopy as well as being a blessing for necks and spines of endoscopists, along with their assistants they can view the image on a television screen instead of looking through a keyhole. Since then, the endoscopes design has been relatively static, and the changes introduced aimed mostly an improvement in image capabilities, with the addition of an array of technologies like ultrasound (Strohm at al. 1980), high-quality optical discrimination and zooming (Nelson et al. 2000), narrowband illumination (Song et al. 2008) and confocal microscopy (Kiesslich et al. 2009).

All this technological evolution, mainly the development of fully flexible gastrointestinal endoscopy recreates the gastroenterology as a specialty. The last 40 years made an enormous impact on gastroenterological practice, what resulted from the intrinsic value of the information provided by endoscopy and the ease with which it can be acquired, transmitted and applied (reviewed by Modlin 2000). It made possible the understanding of many diseases including the gastro-esophageal reflux, gastritis, NSAID injury, gastrointestinal bleeding, gastrointestinal tract cancers, pancreatic and biliary disease, to name just a few. It was also the routine application of endoscopic biopsy that ultimately led to the discovery of Helicobacter pylori, changing the pathophysiological concept of ulcer disease (Marshall 2008). Endoscopy has meshed well with pathology and with developments in radiographic and ultrasound techniques, resulting in rapid advances in diagnosis and treatment.

1.2 – ENDOLUMINAL ENDOSCOPIC SURGERY

The GI endoscopy initially started with a diagnosis purpose, but the diagnostic equipment became the platform for powerful therapeutic tools (Ponsky 2006). Approaches to gastrointestinal bleeding were soon introduced, including the use of monopolar and bipolar probes, injection therapy and clip application (Gaisford 1979). These methods became extremely successful and changed the treatment of patients with hemorrhage, greatly reducing the need for emergent surgery. For colon, colonoscopy evolved quickly to permit identification and marking of neoplasia as well as extraction of the majority of polyps (Shinya et al. 1976). The polyp-cancer sequence was defined, and the value of screening colonoscopy with polyp removal was demonstrated.

In the 1970s the ERCP became widely practiced to permit access to the bile duct for removal of stones and decompression of obstruction (Kawai et al. 1974). With the addition of intraluminal stenting, the treatment of benign and malignant conditions has continued to advance, metal self-expanding prostheses are increasingly used for malignant obstruction whereas biliary or pancreatic benign leaks, after trauma, pancreatitis or cholecystectomy, are treated with plastic stents.

In what would be thought to be a risky-procedure, a pediatric surgeon described successfully the combined endoscopic and percutaneous placement of a gastrostomy tube extended the endoscopic paradigm outside the GI tract (Gauderer et al. 1980), whereas endoluminal approaches have been used alone or in combination with laparoscopy to drain pseudocysts and necrosis of the pancreas and to excise stromal tumors (Kozarek 1985; Rosen et al. 2005). Otherwise, gastrointestinal obstruction and stenosis attributable to benign or malignant conditions has been treated successfully with endoscopic dilation and enteric stents that became more and more sophisticated with different materials and covertures depending on the purpose (Simmons et al. 2005). In case of malignancy stenting it provides a palliative approach, but also a bridge to programmed surgery, mainly in colon.

Currently, all areas of endoscopic practice have advanced and become highly sophisticated. In the upper GI tract, esophageal varices are routinely treated with banding and injection therapy. Barrett's esophagus is being carefully evaluated with a variety of image methods and new efforts at its ablation and excision are being applied, including photodynamic therapy, radiofrequency, and partial or complete endoscopic mucosal resection (reviewed by Johnston 2005; Bergman 2006). Mucosal resection also is being applied to premalignant and early malignant lesions of the esophagus, stomach and colon, obviating the need for surgery in many cases (Ono et al. 2005). Endoscopic ultrasound has become an invaluable tool for assessing the nature of such lesions and the depth of their penetration. With needle biopsy and injection techniques, the utility of endoscopic ultrasound has been extended to outside the GI area, for pseudocyst drainage, celiac plexus block and injection of substances into tumors (Dancygier et al. 1999).

Ultimately exciting new areas of endoluminal therapeutic endoscopy hold great promise for the future: the anti-reflux interventions, like peroral fundoplication, the bariatric procedures, like Toga sleeve, and the widespread submucosal dissection, increasingly used for treatment of early neoplasia in the esophagus, stomach and colon (reviewed by Reavis and Melvin 2008). The gastrointestinal tract becomes progressively, and almost completely, accessible for diagnosis and intervention using endoluminal endoscopy through the mouth or the anus, its natural orifices.

1.3 – TRANSLUMINAL ENDOSCOPIC SURGERY

Paralleling the previous description, endoscopy has also been used to access corporal cavities through the external wall in a percutaneous mode, the denominated laparoscopy. The true interest on that approach emerged after the French gynecologist Mouret carried out the first acknowledged laparoscopic cholecystectomy, using four trocars, in 1987 (Mouret 1991). Laparoscopic cholecystectomy soon became the gold standard, and nowadays almost all procedures with exception of transplantation can be done laparoscopic or thoracoscopically with many proven advantages for the patient, over traditional open procedures, such as minimal scarring, reduced pain and faster recovery (reviewed by Davis 1992), this highlight the end of the "big incision, great surgeon" time and the beginning of the minimally invasive surgery (MIS) era.

It is clear now that gastroenterologists are becoming progressively more invasive, whilst much of surgery has become less so. The actors on the digestive stage - minimally invasive surgeons and interventional gastroenterologists - now look very similar (Cotton 2000). They work guided by endoscopic images with complex instruments passed through small holes in their patients, the surgeon on the peritoneal side and the gastroenterologist on the endoluminal space, separated by the wall barrier.

Some pioneers have literally jumped "out of the box" by driving their flexible endoscopes through the gastric wall into a whole new world. In 2003, Reddy and Rao, and Kalloo et al in 2004 reported an innovative concept of accessing the peritoneal cavity by perforating the stomach wall, giving support for the birth of Natural Orifice Transluminal Endoscopic Surgery (NOTES) (Kalloo et al. 2004). At that time, this represented a controversial dogma rupture - the breaching of the gastrointestinal barrier could switch from a complication to an advantage, and that was a step much forward than the intents beneath the pseudocyst drainage and the percutaneous endoscopic gastrostomy started, respectively, 30 and 25 years before. After the launching of natural orifice transluminal concept many researchers ensue fascinated once many advantages were immediately predicted. Laparoscopic surgery has taught us that smaller incisions are associated with faster recovery, earlier return to work, and less suppression of the immune response with fewer adhesions. From the standpoint of invasiveness, it seemed that NOTES was the natural convergence of laparoscopic surgery and therapeutic endoscopy, and it was reasonable to think that it may further improve on the benefits of laparoscopy.

This emergent surgical territory pushed the creation of an initial consortium (NOSCAR) with the aim of assess and research on NOTES (Rattner and Kalloo 2006). The analysis made by leaders in the fields of endoscopy and surgery exposed some potential barriers to clinical practice: i) safe access to peritoneal cavity; ii) gastric closure; iii) prevention of infection; iv) development of suturing device; v) spatial orientation; vi) stable multitasking platform to obtain adequate anatomy exposure, organ retraction, secure grasping and triangulation; vii) difficulty in controlling the pneumoperitoneum; viii) management of iatrogenic intraperitoneal complications. They demanded further controlled studies to surmount these limitations.

In a short period of time, several experimental surgical laboratories working in pigs exposed their experience in an array of abdomino-pelvic procedures by transgastric approach, and started to explore others natural orifices. Lima et al assessed the feasibility and safety of a transvesical approach to the peritoneal cavity, and confirmed that it was the most anterior-inferior access allowing the introduction of rigid or flexible instruments up to 5 mm, with the advantage of being naturally sterile (Lima et al. 2006). Subsequently were described the transcolonic (Pai et al. 2006) and transesophageal (Sumiyama et al. 2007) ports, and the transvaginal approach (Deker 1954), an older access used by gynecologists, was re-discovered.

Chapter 2.
Rationale for Peroral NOTES & Subsequent Studies

Patients are bound to choose the less invasive and less painful medical interventions. They are right to do so and it is incumbent on us as doctors trying to help their aspirations to become a reality. So the three main justifications for NOTES are improved cosmetic appearance, reduced discomfort, and the concept that human ingenuity and technological advance can continue to reduce the trauma and discomfort associated with effective surgery (Swain 2008).

The most important for the patient is the improved cosmetic result and it is not just a matter of vanity. The scars from laparoscopy and thoracoscopy are not invisible and can be very unsightly. Surgery that avoids scars means that patients do not have a visual reminder of the episode every time they undress, the so called "invisible mending". Simultaneously if there is no incision through the wall skin and muscle, and knowing that viscera are not sensible to cut, is expectable that NOTES would be less painful. This would be particularly important in thorax approach, where the even small incisions cause important intercostals nevralgia. Otherwise it is proposed that this kind of approach would be even optionally preferable for certain patients (Swain 2008; Giday et al. 2007): i) obese patients; ii) patients with abdominal sepsis; iii) patients with abdominal wall burn scars or incisional hernia; iv) patients unfit for anesthesia or critically ill.

As it has been described, the peroral approach to the abdomen, using the stomach as an ingress organ, instigated all this revolution and many investigators tested the feasibility of the transgastric access for different surgical procedures, such as fallopian tube ligation (Jagannath et al. 2005), cholecystectomy and cholecystogastric anastomosis (Park et al. 2005; Swanström et al. 2005), gastrojejunostomy (Kantsevoy et al. 2005), oophorectomy (Wagh et al. 2006), lymphadenectomy (Fritscher-Ravens et al. 2006) and splenectomy (Kantsevoy et al. 2006). These studies identified four fundamental challenges: the access creation, the prevention of infection, the tissue manipulation (traction and triangulation) and the gastrotomy closure. Otherwise transgastric port seems to have a few benefits as a NOTES peritoneal access, like good vascularization and healing, partial sterility, the possibility of specimen retrieval, and a privileged upper position.

After the initial transgastric excitement, Sumiyama et al tested the peroral approach for thorax exploration, describing the transesophageal access (Sumiyama et al. 2007). By using the esophagus as an entry site, direct access to the thorax and particularly to the posterior mediastinum was allowed, with several potential indications (Clark et al. 2009). Even if the general concept might be appealing, this seems to be the most transgressive approach in the NOTES world. It may pose greater risk for mechanical abrasion and trauma of surrounding structures, and in addition, the consequences of a leak from an esophageal enterotomy would be particularly devastating for the patient. In this sequence, the known unsolved problems of NOTES appear even more unacceptable in the transesophageal approach.

Thus, taking into account the described potentialities of the peroral surgery and the limitations for NOTES humans' translation, we planed our experimental studies and the aiming of this PhD thesis in order to deal and overcome some of them.

Chapter 3.
Aims

1. **To optimize technical aspects of the transgastric port and to test the feasibility, safety and benefits of its combination with another natural orifice access:**
   a) Training and amelioration of the transgastric port
   b) Selection of the most adequate supplementary port and test two natural orifice ports creation, coordination, benefits and risks

2. **To evaluate the feasibility and usefulness of the transgastric and transvesical combined approach in different grades of surgical complexity:**
   a) Assess the practical overcoming of technical problems previously described for isolated transgastric cholecystectomy (a moderately complex procedure) and nephrectomy (a more complex procedure)
   a) Infer practical implications from different natural orifices approaches, comparing an upper versus a lower abdominal port

3. **To describe novel surgical techniques for common procedures:**
   a) Description of NOTES cholecystectomy combined approach
   b) Description of NOTES transgastric varicocelectomy
   c) Peroral esophageal resection and anastomosis

4. **To test a new endoscopic method for gastrotomy closure:**
   a) Evaluation of the in vivo system appliance and safety in survival studies

5. **To propose an intermediate step for thoracic NOTES humans translation**
   a) Test the *ex-vivo* and *in-vivo* feasibility of an esophageal anastomosis using the transesophageal access with assistance of a single transthoracic trocar

PART II
results

Chapter 4. Cholecystectomy by Transgastric & Transvesical Combined Approach

Third Generation Cholecystectomy by Natural Orifices: Transgastric and Transvesical Combined Approach

Rolanda C, Lima E, Pêgo JM, Henriques-Coelho T, Silva D, Moreira I, Macedo G, Carvalho JL, Correia-Pinto J.

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Searching the Best Approach for Third Generation Cholecystectomy

Rolanda C, Lima E, Correia-Pinto J.

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ORIGINAL ARTICLE: Experimental Endoscopy

Third-generation cholecystectomy by natural orifices: transgastric and transvesical combined approach (with video)

Carla Rolanda, MD, Estêvão Lima, MD, José M. Pêgo, MD, Tiago Henriques-Coelho, MD, David Silva, MD, Ivone Moreira, Guilherme Macedo, MD, PhD, José L. Carvalho, MD, Jorge Correia-Pinto, MD, PhD

Braga, Portugal

Background: An isolated transgastric port has some limitations in performing transluminal endoscopic cholecystectomy. However, transvesical access to the peritoneal cavity has recently been reported to be feasible and safe.

Objective: To assess the feasibility and the technical benefits of transgastric and transvesical combined approach to overcome the limitations of isolated transgastric ports.

Design: We created a transgastric and transvesical combined approach to perform cholecystectomy in 7 consecutive anesthetized female pigs. The transgastric access was achieved after perforation and dilation of the gastric wall with a needle knife and with a balloon, respectively. Under cystoscopic control, an ureteral catheter, a guidewire, and a dilator of the ureteral sheath were used to place a transvesical 5-mm overtube into the peritoneal cavity. By using a gastroscope positioned transgastrically and a ureteroscope positioned transvesically, we carried out cholecystectomy in all animals.

Results: Establishment of transvesical and transgastric accesses took place without complications. Under a carbon dioxide pneumoperitoneum controlled by the transvesical port, gallbladder identification, cystic duct, and artery exposure were easily achieved in all cases. Transvesical gallbladder grasping and manipulation proved to be particularly valuable to enhance gastroscope-guided dissection. With the exclusion of 2 cases where mild liver-surface hemorrhage and bile leak secondary to the sliding of cystic clips occurred, all remaining cholecystectomies were carried out without incidents.

Limitations: Once closure of the gastric hole proved to be unreliable when using endoclips, the animals were euthanized; necropsy was performed immediately after the surgical procedure.

Conclusions: A transgastric and transvesical combined approach is feasible, and it was particularly useful to perform a cholecystectomy through exclusive natural orifices. (Gastrointest Endosc 2007;65:111-7.)

Since the first reports in the late 1980s, laparoscopy has progressively become the criterion standard for cholecystectomy, one of the most widely performed abdominal interventions in developed countries. In fact, minimally invasive surgery is now associated with many proven advantages over traditional open procedures, such as minimal scarring, reduced pain, and faster patient recovery.[1]

In parallel with the progression of minimally invasive surgery, improvements in endoluminal endoscopy have made it an indispensable and multifaceted instrument for diagnosis and, definitively, for therapy.[2] Recently, Reddy and Rao (N. Reddy, V. G. Rao, oral communications, May 2005; N. Reddy, oral communication, May 2004), in human beings, and Kalloo et al,[3] in a porcine model, described a new port to the peritoneal cavity through a transgastric approach. Subsequently, various investigators described more complex intra-abdominal procedures in porcine model,[4-12] opening a new era in the surgical field in what seems to be the third-generation surgery: natural orifice transluminal endoscopic surgery (NOTES).[13]

Park et al[5] conducted the first pilot study in pigs by applying NOTES to perform transgastric cholecystectomy. By using 2 endoscopes or a single endoscope conjugated with a transabdominal trocar, cholecystectomy was feasible, but important limitations were identified. These were related to difficulty in controlling the pneumoperitoneum and in obtaining a stable platform for anatomy exposure, organ retraction, secure grasping, and adequate

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triangulation of instruments. Swanström et al[12] attempted to overcome these limitations by using ShapeLock technology (USGI Medical, San Clement, Calif) as a new overtube for transgastric surgery. However, even with this equipment, an isolated transgastric approach for gallbladder manipulation remained a challenge, with only a 33.3% success rate.[12]

These studies were able to demonstrate that cholecystectomy may one day be performed without skin incisions. The development of other natural orifice accesses, however, may play an important role in overcoming some of the limitations identified for those who performed abdominal surgery through isolated transgastric surgery.[13] By applying these concepts, Lima et al[14] demonstrated that transvesical endoscopic peritoneoscopy was technically feasible and could be safely performed in a porcine model. By using a transvesical port, it was possible to introduce 5-mm rigid instruments, such as graspers, scissors, and telescopes. We hypothesized that a transvesical port could be useful to perform abdominal procedures in combination with a transgastric pathway.

The purpose of this experimental study was to assess the feasibility and the technical benefits of a combined transgastric and transvesical approach for cholecystectomy in a porcine model.

Capsule Summary

What is already known on this topic

- Transgastric cholecystectomy is feasible in a porcine model, but it has limitations that jeopardize its clinical application, including difficulty in controlling the pneumoperitoneum and in securing a stable platform for anatomy exposure, organ retraction, secure grasping, and adequate instrument triangulation.

What this study adds to our knowledge

- In 7 pigs, gallbladder identification and cystic duct and artery exposure were achieved by using transvesical and transgastric access; transvesical gallbladder grasping and manipulation was particularly useful in gastroscope-guided dissection.

MATERIALS AND METHODS

This was a nonsurvival study approved by the ethical review boards of Minho University (Braga, Portugal). For this study, we included 15 small (15-25 kg) female pigs (*Sus scrofus domesticus*) so that the current ureteroscope length could easily achieve the upper-abdominal organs. After a significant surgical and anesthetic learning curve, the results of which are not included in this report (9 animals), we performed the cholecystectomy exclusively through natural orifices (transgastric and transvesical combined approach) in 7 consecutive animals. After the surgical procedures, the animals were euthanized, and necropsies were performed.

Pig preparation

The animals were fed liquids for 3 days and then were restrained from food (24 hours) and water (6 hours) before the surgical intervention. All procedures were performed with the pigs under general anesthesia, with 5.0-mm endotracheal intubation and mechanical ventilation. Preanesthesia medication consisted of an intramuscular injection of 32 mg/mL azaperone (Stressnil; Esteve Farma, Barcelona, Spain) reconstituted with 1 mg/mL midazolam (Dormicum; Roche, Amadora, Portugal) at a dose of 0.15 to 0.2 mL/kg.

Venous access was obtained through an intravenous line placed in the marginal ear vein. Anesthesia was induced with 3 μg/kg fentanyl (Fentanest; Janssen-Cilag, Queluz, Portugal), 10 mg/kg thiopental sodium (Pentothal; Abbott, Alfragide, Portugal), and 1 mg/kg vecuronium (Norcuron; Organon, Oss, The Netherlands). Anesthesia was maintained with 1.5% to 2% sevoflurane (Sevorane; Abbott) and a perfusion of 1 mg/kg per hour of vecuronium. All animals received an intramuscular injection of 1 g ceftriaxone (Rocephin; Roche) before beginning the surgical procedures.

Surgical technique

Transvesical access. Creation of a transvesical access is illustrated in Video 1 (available online at http://www.giejournal.org). An ureteroscope (A2942A; Olympus, Tokyo, Japan) was introduced through the urogenital sinus and the urethra into the bladder with hydrodistension. Before any further procedure, the bladder was emptied of urine and refilled with saline solution. The vesicotomy site was carefully selected on the ventral bladder wall, posterior to the bladder dome. A mucosal incision was made with a scissors (A2576; Olympus) introduced by the working channel of the ureteroscope. Subsequently, a 5F open-end ureteral catheter (Selectip, 62450200; Angiomed, Bard, Murray Hill, NJ) was pushed forward through the incision into the peritoneal cavity. A 0.035-inch flexible-tip guidewire (RF*GA35153M, Terumo Corp, Somerset, NJ) was then inserted into the peritoneal cavity through the lumen of the ureteral catheter. Guided by the flexible-tip guidewire, the vesical hole was enlarged with a dilator of an ureteroscope sheath (250-105; Microvasive Endoscopy, Boston Scientific Corp, Natick, Mass), which was enveloped with an overtube designed by us (25-cm length, 5.5-mm internal diameter, and 1-mm wall thickness). A rigid ureteroscope was introduced into the peritoneal cavity within the overtube and allowed the creation of a pressure-controlled carbon dioxide (CO_2) pneumoperitoneum up to 12 mmHg. Through the overtube, we could insert into the peritoneal cavity either a video telescope with

5-mm diameter, chip-on-the-tip, and 0-degree view direction, normally used as a laparoscope (EndoEye 50021A; Olympus) or a rigid ureteroscope that includes a working channel. The peritoneal cavity was thoroughly examined, with particular emphasis on the stomach, the liver, and the gallbladder.

Transgastric access. An adult forward-viewing, double-channel endoscope (GIF-2T160; Olympus) was advanced into the esophagus and the stomach. The stomach was lavaged with instilled water and was aspirated through the gastroscope until free of food particles. Subsequently, it was decompressed and a cefazolin solution (1 g in 200 mL saline solution) was instilled. The antibiotic solution was left in the stomach for 10 minutes before also being aspirated. For the gastrotomy-site selection and to avoid damage of the gastric vessels or surrounding organs, the gastroscope operator was working with both internal (provided by the gastroscope observing the internal stomach indentation produced by external abdominal palpation) and external (provided by the EndoEye or ureteroscope) gastric-wall images. The gastrotomy site was carefully chosen on the anterior wall (body-antrum transition). A gastric-wall incision was made by pushing forward a needle knife, followed by its sheath (KD-11Q-1; Olympus) with cautery (PSD 20; Olympus) under a 12 mmHg CO_2 pneumoperitoneum (induced through the transvesical port). The needle-knife sheath was then used for positioning a guidewire (5156-01; Microvasive Endoscopy). The puncture dilation was performed with an 18-mm through-the-scope balloon (5837; Microvasive Endoscopy) over the guidewire. On balloon semideflection, the gastroscope was pushed forward and passed into the peritoneal cavity. All these procedures were monitored by the scope positioned through the transvesical port.

Cholecystectomy surgical procedure

After establishment of the 2 diametrically opposed ports (transgastric and transvesical) and CO_2-pneumoperitoneum creation, the ureteroscope easily identified the gallbladder. A forceps was then passed through the ureteroscope working channel, and the gallbladder fundus was grasped and upward retracted. This maneuver nicely exposed the gallbladder infundibulum and the cystic duct. Subsequently, the gastroscope was moved on retroflexion toward the gallbladder. The exposure achieved by the transvesical gallbladder grasping allowed the gastroscope operator to quickly identify the cystic duct. This allowed us to start careful dissection, handling either a grasping forceps (FG-6L-1, FG-47L-1; Olympus) or a 2.8-mm ball coagulation electrode (CD-1U; Olympus) passed through the working channels of the gastroscope. For this purpose, we also had available a pre-cut needle knife (KD-11Q-1; Olympus) and a scissors (FS-5L-1; Olympus). Both sides of cystic duct were completely dissected by alternating the working channels of the grasping forceps and the coagulation electrode. When the cystic duct and artery were dissected and free, 3 clips (HX-200L-135; Olympus) were applied: 2 on the gallbladder extremity and the other proximally. Sectioning of pedicle was then carried out with a needle knife. The grasping provided by the ureteroscope allowed us to retract the gallbladder body in the major axis (up and down; right and left), looking for the most appropriate anatomical exposure for dissection. Small position adjustments were also possible when using the forceps introduced by the gastroscope. Blunt dissection was taken progressively by electrocautery of the gallbladder bed. When cholecystectomy was completed, the gastroscopic forceps held the cystic-duct extremity distally to clips, and the gallbladder was removed via the esophagus and the mouth.

RESULTS

All procedures involved in the creation of the vesical hole (cystoscopy, bladder mucosal incision, vesicotomy, transvesical overtube passage) were performed without complications. The ureteroscope was easily introduced into the peritoneal cavity, and insufflation of CO_2 was performed without incident. By using the transvesical port, we could obtain a perfect view of the upper-abdominal organs (liver, gallbladder, stomach, spleen, and diaphragm). This was particularly useful in helping the gastroscope operator to safely perform the gastrotomy.

Under a CO_2 pneumoperitoneum and with the view provided by the transvesical port, we created the gastrotomy in a rapid, safe, and easy way. In fact, with our approach, neither gastric vessels nor surrounding organs were damaged. In addition, the ureteroscope was extremely useful many times in assisting the passage of the gastroscope through the gastrotomy.

Gallbladder identification was easily achieved in all experiments, first, by the ureteroscope. After gallbladder fundus grasping with transvesical instruments, the gastroscope easily identified the cystic duct in all cases (Fig. 1). Under transvesical gallbladder retraction, gastroscopic dissection (Fig. 2), isolation, clipping, and sectioning (Fig. 3) of the cystic duct and artery was feasible and, therefore, was performed in a precise way in all cases. For these purposes, we successfully used a grasping forceps and a coagulation electrode inserted through the gastroscope working channels. A pre-cut needle knife and scissors were rarely applied in these procedures. After sectioning of the clipped cystic duct and artery, we began a dissection of the gallbladder from its bed by using the coagulation electrode (Fig. 4). This proved to be the most fastidious and, simultaneously, the most challenging part of the surgery, because the gallbladder body is commonly hidden in the liver parenchyma in pigs. Nevertheless, the transvesical grasping allowed significant manipulation of the gallbladder (Fig. 5), which was particularly useful in

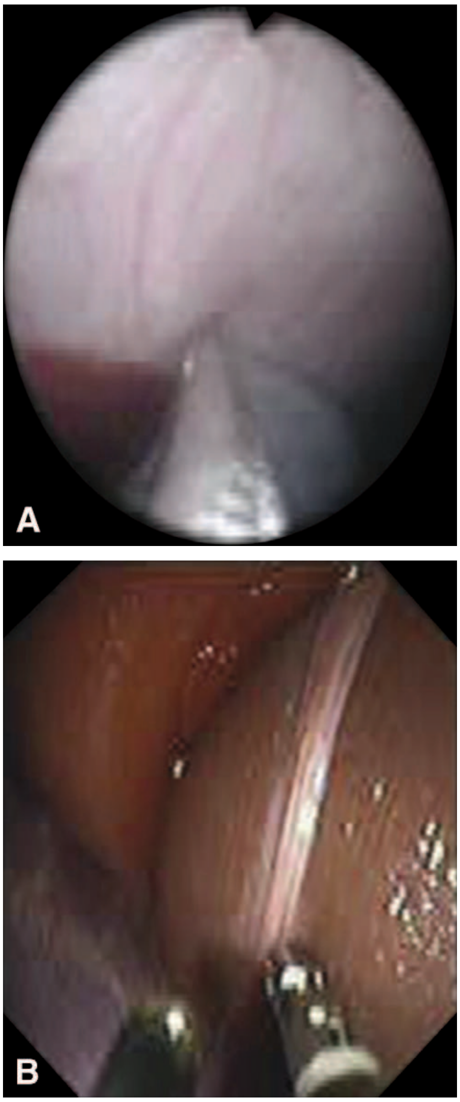

Figure 1. Exposure of cystic duct and artery. **A,** Ureteroscope image: the ureteroscopic forceps holds the gallbladder fundus. **B,** Gastroscope image: transvesical gallbladder retraction exposes the cystic duct and artery for the gastroscope.

selecting the best position for the gastroscope-guided dissection. Liver-surface bleeding occurred in only one case, where an oozing hemorrhage, which did not obscure endoscopic visualization, became significant after relief of the gallbladder upward retraction. We also reported the sliding of a cystic clip and a secondary bile leak as a complication in another case, but, in this circumstance, bubbles from bile spillage seriously disturbed endoscopic view.

Coordination of gallbladder transvesical-transgastric manipulation proved feasible, with rapid progress during the protocol. Similarly, gallbladder withdrawal and retrograde mouth exteriorization were easily achieved with a grasper through the gastroscope. The median time for

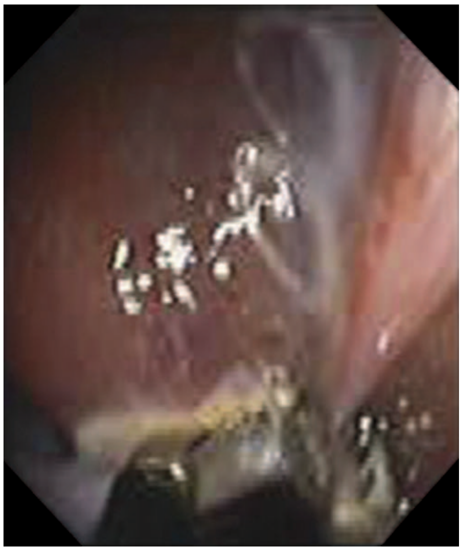

Figure 2. Dissection of the cystic duct and artery. After upward gallbladder retraction (by transvesical port), small position adjustments were possible by using the forceps introduced by the gastroscope.

the overall procedure, including establishment of transvesical and transgastric ports, was 2 hours.

During preliminary experiments performed before starting this study, the closure of a gastric perforation with endoscopic clips were shown, to us, to be unreliable. For this reason, we did not carry out any attempts of gastric closure, and all the animals were euthanized at the end of the cholecystectomy procedure. Necropsies did not reveal any damage of the intraperitoneal organs related to the transgastric or transvesical access and manipulation, except mild hemoperitoneum and bile peritoneal spillage in the above referred cases. The gastric holes measured, on average, 15 mm.

DISCUSSION

Almost 20 years after the first human laparoscopic cholecystectomy, a procedure that was initially viewed with skepticism, many advances have occurred in surgery.[1] Similarly, with the recent unexpected success of a transgastric approach in porcine model,[3-12] an exciting new frontier in minimally invasive surgery was born and is reenergizing the surgical world: NOTES. Whereas, laparoscopic advantages over the open cholecystectomy are well recognized, many potential benefits of cholecystectomy by NOTES over laparoscopy are predicted: (i) avoidance of abdominal scars; (ii) less painful procedure; (iii) possible avoidance of general anesthesia; (iv) probably a preferable approach for morbid obese patients or with scars, burns, and infections in the abdominal wall; and (v) avoidance of postoperative hernias.

When trying to reproduce previous descriptions of transgastric cholecystectomy,[5] we experienced several

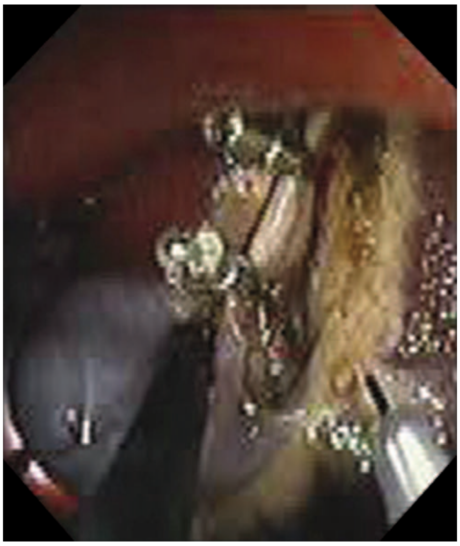

Figure 3. Cystic duct and artery clipping. After cystic duct and artery dissection, endoscopic clips were easy to apply allowing sectioning by a needle knife.

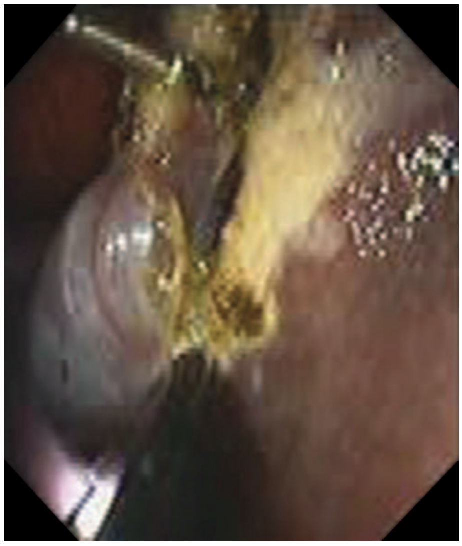

Figure 4. Beginning of gallbladder-bed dissection. By using electrocautery, gallbladder bed dissection was carefully undertaken step-by-step.

problems, as highlighted by others.[5,12] This gave us the rationale to predict that an additional transvisceral port diametrically opposed to the stomach would be helpful in performing complex upper-abdominal endoscopic procedures. In this sequence, we recently proved that a transvesical access through a 5-mm port was technically feasible and safe in a survival porcine model.[14] In the current study, we tested the feasibility and the technical utility of using 2 opposed ports; rigid instruments were used in one to perform cholecystectomy.

Gallbladder identification and cystic pedicle exposure have been reported as a challenge when using an exclusive transgastric port.[5,7,12] Interestingly, with our approach, we could easily identify the gallbladder and expose the cystic duct and artery in all cases. In fact, the frontal view provided by the transvesical access was a determinant for these achievements, because it allowed us to rapidly identify gallbladder fundus, usually without needing special transgastric intervention. Furthermore, the gallbladder upward retraction accomplished by the transvesical operator easily exposed the cystic duct and artery for the gastroscope.

Efficient gallbladder retraction was clearly enhanced by using rigid instruments through the transvesical port. The possibility to introduce rigid instruments with direct handling reinforces the role of a transvesical port in NOTES procedures. One of the major limitations of transgastric surgery was the inexistence of a stable platform that permits organ retraction and triangulation for gallbladder dissection and manipulation.[13,15] This limitation was attributed to the flexibility of current gastroscopes that avoid robust grasping and retraction. In fact, we also had an opportunity to verify that the gastroscope in the retroflexion position and unsupported in the pneumoperitoneum was unreliable for simultaneously exerting organ retraction and dissection. To overcome this limitation, Park et al[5] used either an additional gastroscope or a transabdominal trocar, whereas Swanström et al[12] used flexible multilumen guides that can be locked in position. Even in these circumstances, cholecystectomy was accomplished in only 33% of the attempts. Our transvesical port allowed the passage of a rigid forward-viewing instrument with a forceps that permitted efficient grasping and retraction. In addition, it made it possible to mobilize the gallbladder in various axes, exposing different areas for gastroscope-guided dissection. This partially overcame the absence of triangulation experienced when using only a transgastric port. Although we still needed to work in a retroflexion position, the good exposure achieved by coordinated movements of transvesical devices allowed us to straightforwardly use instruments through both the gastroscope working channels, minimizing the need of gastroscope-dependent grasping.

Another advantage of using the transvesical port was the possibility to work under a pressure controlled CO_2 pneumoperitoneum. This overcomes some common consequences of pneumoperitoneum created by the gastroscope, such as the detrimental action of high ($>$15 mm Hg) intraperitoneal pressures, the augmented combustion risk, and the slower air reabsorption rate.[13] In fact, insufflation provided by current flexible endoscopes is neither pressure controlled nor uses CO_2.

Insufflation of the pneumoperitoneum before gastrotomy creation proved useful in preventing undesired damage of gastric vessels and adjacent organs. In addition, with the transvesical image, we could monitor all procedures involved in the gastrotomy creation. Unintended and unrecognized laceration of adjacent organs is a major

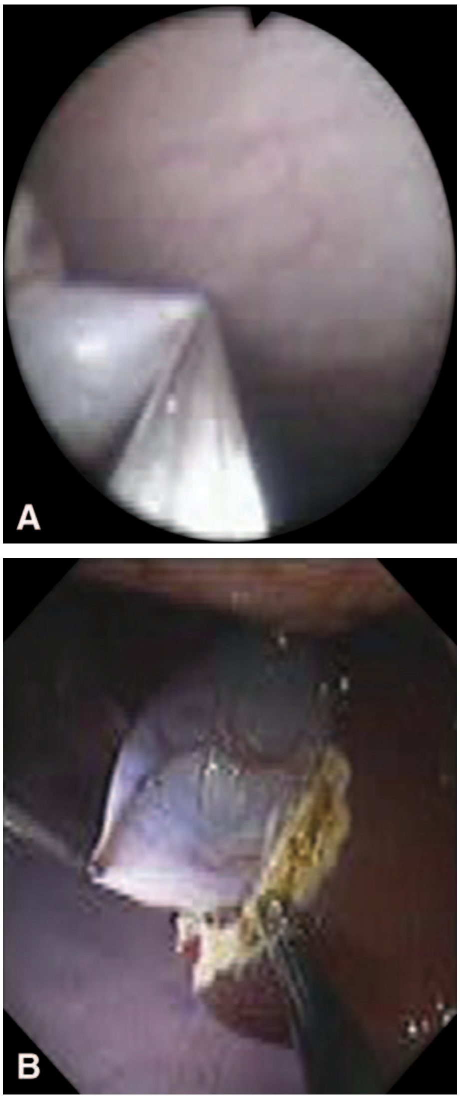

Figure 5. Coordinated transgastric-transvesical approach. **A,** Ureteroscope image, and **B,** gastroscope image, illustrating how transgastric and transvesical combined approach can easily mobilize the gallbladder.

concern reported by investigators dealing with transgastric approach.[16] In fact, there are descriptions of liver and anterior abdominal-wall trauma during gastrotomy.[10] The CO_2 pneumoperitoneum and the open front view provided by the transvesical port allowed the displacement of the abdominal wall from the stomach and provided a good in-time control of the gastric exit of the gastroscope, making the procedure more rapid and safe. The risk of adjacent structure damage was not a problem during the creation of transvesical port, because it is created with atraumatic instruments and without electrocautery. In addition, because bowel loops in contact with the bladder wall (small intestine and sigmoid colon) are free in the abdomen, they run ahead of the ureteral catheter atraumatic tip.

Although this study reinforces that NOTES cholecystectomy is feasible, some important technical pitfalls remain unsolved. Gastric closure is likely the most important issue limiting widespread translation of NOTES for human beings. Although, we attempted to reproduce the technique of endoclip gastric closure executed by several investigators,[3,5,7,10,11] we realized that endoclip application (currently available) was fastidious and cumbersome, with unreliable results and poor safety. This was the reason that we did not go forward with survival studies. We do not exclude the hypothesis that our technique for gastric perforation (balloon dilation) disturbed the conditions for clip application. In fact, we recognize that if dilation is efficient in maintaining muscle integrity for contraction, the cutting electrocautery would define more regular borders for tissue approximation. Even knowing gastric injuries heal quickly and that survival studies have been done, without any maneuver for gastric closure, with surprising good results,[4] we believe that this is a major drawback that might risk the technique accreditation if not correctly surmounted. With regard to a transvesical port, we previously demonstrated in a survival study that a 5-mm transvesical hole closes spontaneously without complications in a porcine model.[14] Bladder decompression by a vesical catheter and the healthiness of the bladder wall explain why vesicotomy suturing may not be necessary.

The risk of infection should not be neglected. Although neither bladder nor stomach are physiologically infected, the routes followed by the scopes may contaminate them. The development of appropriate overtubes, as already used by others[4,11] for transgastric surgery, might significantly minimize this risk.

During our experiments with a transvesical port, we detected that the current instruments are too short to reach the upper abdomen. In our study, we dealt with this problem by using smaller animals, but we feel that biomedical engineering will need to develop longer instruments if we want to use the transvesical port in adult human beings.

In conclusion, this study demonstrated the usefulness of combining 2 natural orifices (transgastric and transvesical) ports in moderately complex abdominal surgical procedures, eg, cholecystectomy. The addition of the transvesical port overcame most of the limitations previously reported for those who attempted to perform cholecystectomy exclusively through a transgastric approach. This study reinforces the feasibility of exclusive natural orifices transluminal endoscopic cholecystectomy.

ACKNOWLEDGMENTS

We thank Mr Paulo Pereira and Mr José Bragança (Ethicon EndoSurgery, Portugal) for their assistance in this project.

DISCLOSURE

The authors have no conflict of interest to disclosure.

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LETTERS TO THE EDITOR

Searching the best approach for third-generation cholecystectomy

To the Editor:

We carefully read the study from Pai el al[1] that demonstrates the technical feasibility of transcolonic cholecystectomy. Recently, we also investigated an endoscopic approach to perform scarless cholecystectomy through a transgastric and transvesical combined approach.[2] In our study, we also confirmed that an abdominal inferior port provides an en face orientation to the upper abdominal organs and allows better visualization and the ability to work straightforwardly. However, for these purposes, we used a transvesical instead of a transcolonic port. In fact, the transvesical access to the peritoneal cavity was feasible, easy to install, and safe in a survival porcine model study. Moreover, it should be emphasized that we did not experience any complications, such as adhesions or peritonitis, even when we left the vesicotomy point unclosed.[3]

However, previous studies that tried to perform cholecystectomy by natural orifice transluminal endoscopic surgery (NOTES) performed it by using a single port, either transgastric or transcolonic.[1,4,5] These approaches share common limitations, such as difficulties in performing effective retraction and dissection with triangulation. In fact, we should not forget that cholecystectomy is a moderately complex procedure, usually needing 4 to 5 trocars in the laparoscopic technique. To deal with these limitations, we combined 2 diametrically opposed ports (transgastric and transvesical), which was particularly useful.[2]

Although these studies clearly reinforce the idea that third-generation cholecystectomy (by NOTES) might be feasible in human beings in the near future, further experimental studies are needed to identify the most appropriate approach.

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Response:

We appreciate the comments of the Correia-Pinto team regarding our article on transcolonic NOTES cholecystectomy and look forward to their upcoming publication involving a unique transvesical approach. Their work appears to confirm the advantages of working in an enface position as provided by an inferior peritoneal access site. Additionally, they emphasize the benefits of diametrically opposed ports.

We too have dabbled with simultaneous ports; however, we utilized gastric and colonic access sites (referred to as the ‘‘rotisserie method’’ by some in our laboratory). The extra port may be advantageous in providing traction and occasionally may present a better angle for dissection; however, we would hope not to rely on this for most procedures in the future. If an additional port is essential to complete a given procedure, it may be more suitable to use micro-trochars rather than a second site of luminal breach, until other options are available. Also, just as different

Chapter 5. Nephrectomy by Transgastric & Transvesical Combined Approach

Third Generation Nephrectomy by Natural Orifice Transluminal Endoscopic Surgery

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J Urol 2007; 178:2648-2654.

Third-Generation Nephrectomy by Natural Orifice Transluminal Endoscopic Surgery

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Purpose: Recently there has been increasing enthusiasm for performing simple abdominal procedures by transgastric surgery. We previously reported the usefulness of a combined transgastric and transvesical approach to cholecystectomy. In this study we assessed the feasibility of combined transgastric and transvesical approach for performing a more complex surgical procedure, such as nephrectomy, in a porcine model.

Materials and Methods: In a nonsurvival study combined transgastric and transvesical approaches were established in 6 female pigs. Under ureteroscope guidance we installed a transvesical 5 mm over tube into the peritoneal cavity and a flexible gastroscope was passed orally into the peritoneal cavity by a gastrotomy. We performed right or left nephrectomy with instruments introduced by the 2 devices that worked in the renal hilum, alternating device intervention for dissection and retraction procedures.

Results: Four right and 2 left nephrectomies were performed. There were no complications during the creation of transvesical and transgastric access. In all animals we visualized the 2 kidneys. The renal vessels and ureter were reasonably individualized and ligated separately with ultrasonic scissors, which were introduced through the transvesical port. In 2 early cases mild hemorrhage occurred after ultrasonic ligation. To overcome this complication we applied clips successfully before ultrasonic ligation in the remaining animals. Thus, complete renal release and mobilization to the stomach were achieved in all animals.

Conclusions: Nephrectomy by natural orifices using the combined transgastric and transvesical approach is technically feasible, although to our knowledge there is no reliable method for removing the specimen with current instruments.

Key Words: kidney; swine; nephrectomy; endoscopy; surgical procedures, minimally invasive

Renal surgery has its origin some 400 years B.C.E. with the drainage of abscesses and the removal of calculi from renal fistulas. In the early 19th century kidneys were sometimes removed inadvertently during attempted ovarian surgery with the observation that the remaining kidney continued to produce normal amounts of urine. However, it was not until 1869 that Simon performed the first planned nephrectomy.[1] During the last century there was progressive development of the surgical technique, aiming mainly at organ resection without apprehension and associated morbidity.

With the first laparoscopic nephrectomy in 1990 performed by Clayman et al a revolution began with the implementation of laparoscopic techniques that had become accepted by the urological community worldwide, initially for benign and more recently for malignant renal disease.[2] The main reasons that minimally invasive surgery increased in popularity were the many proven advantages over traditional open procedures, such as minimal scarring, decreased pain and more rapid patient recovery.[3]

Currently NOTES is being studied as a potentially less invasive alternative to conventional laparoscopy for intra-abdominal surgery. In fact, there is increasing hope that we will be able to perform the most common abdominal procedures in humans using this revolutionary technique that seems to be third-generation surgery. After the development of transvaginal peritoneal access, mainly for specimen extraction,[4] Gettman et al used this approach to perform nephrectomy.[5] More recently transgastric access to the peritoneal cavity was described with unexpected success.[6] Subsequently we had the opportunity to test the feasibility and safety of a transvesical port to the peritoneal and thoracic cavities.[7,8] This port was revealed to be particularly important because some procedures that appeared hazardous and not viable using an isolated transgastric port become feasible and safe when performed by a combined transgastric and transvesical approach, as we recently described for cholecystectomy.[9]

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Study received approval from ethical review boards at Minho University, Braga, Portugal.

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Before translation in humans additional preclinical studies are still needed to increase our confidence with these techniques in high risk procedures such as nephrectomy.[10] We report the feasibility of the combined transgastric and transvesical approach for performing scarless natural orifice nephrectomy in a porcine model.

MATERIALS AND METHODS

This study was approved by ethical review boards at Minho University, Braga, Portugal. After a surgical learning curve of 4 animals (data not shown) right or left nephrectomy was performed in 6 consecutive anesthetized female pigs (Sus scrofus domesticus) weighing 25 to 30 kg. After the surgical procedures the animals were immediately sacrificed and necropsy was performed.

Pig Preparation

The animals were fed liquids for 3 days and then were denied food for 24 hours and water for 6 before surgical intervention. All procedures were performed using general anesthesia, as described previously.[7]

Surgical Technique and Instruments

The technique of performing nephrectomy by NOTES was begun using a transvesical port and subsequently a transgastric port (fig. 1). Through the transvesical port we used a rigid Olympus® A2942A ureteroscope, LCSC5L UltraCision® Harmonic Scalpel® Long Shears ultrasonic scissors or an EL5ML Ligamax™5 clip applicator. Through the transgastric port an adult, forward viewing, double channel Olympus GIF-2T160 endoscope was introduced. Through the working channels of the 2 endoscopes we used certain instruments, including 1) ureteroscope instruments (Olympus A2574 grasping forceps and Olympus A2576 scissors) and 2) gastroscope instruments (an Olympus KD-11Q-1 needle knife, a Microvasive® 5156-01 guidewire, a Microvasive 5837 through the scope balloon, Olympus FG-6L-1 and FG-47L-1 grasping forceps, a KD-16Q-1 papillotomy knife and a Sensation™ M00562650 endoscopic snare). For cautery we used standard Olympus PSD 20 electrocautery equipment.

Transvesical Access

A transvesical port was established, as previously described by our group.[7] Briefly, a ureteroscope was introduced into the bladder with CO_2 distention. After making a small mucosal incision on the bladder dome we used a 5Fr open end 62450200 Selectip™ ureteral catheter to perform cystotomy. Guided by a 0.035-inch flexible tip RF*GA35153M Terumo® guidewire the vesical hole was enlarged with the dilator of a 250-105 Microvasive ureteroscope sheath, which was enveloped with a 5.5 mm over tube. A rigid ureteroscope was introduced into the peritoneal cavity within the over tube, allowing the creation of pressure controlled CO_2 pneumoperitoneum as necessary. The peritoneal cavity was thoroughly examined.

Transgastric Access

As previously described,[9] we introduced the gastroscope into the peritoneal cavity through a gastrotomy established on the anterior stomach wall. The gastric wall incision was made by a needle knife with cautery and it was then increased using a papillotomy knife. All procedures were monitored using the view provided by the ureteroscope introduced through the transvesical port.

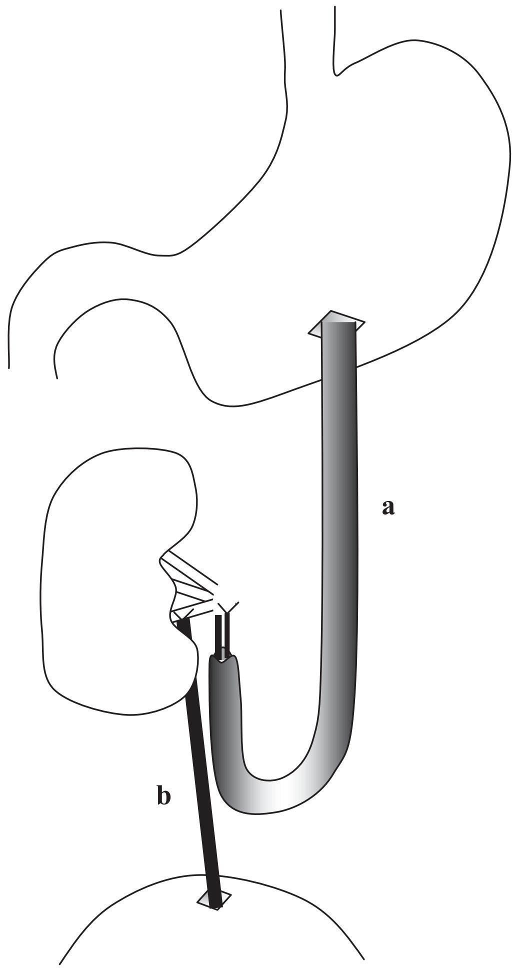

FIG. 1. Instrument positioning for nephrectomy by combined transgastric and transvesical approach. *a*, gastroscope in retroflexion approaching renal hilus. *b*, ureteroscope.

Nephrectomy Procedure

The animals were placed in the lateral decubitus position at the beginning of the procedure to expose the contralateral kidney. Subsequently the selected kidney and respective hilum were immediately identified by the 2 endoscopes. We then mobilized the lower kidney pole by opening the parietal peritoneum with cautery using the needle knife introduced by the gastroscope. This procedure was helped by suspending the peritoneum using grasping forceps introduced through the working channel of the ureteroscope. Subsequently the peritoneum was reflected off the kidney hilum by serial combined actions of the grasping forceps and a needle knife introduced through the ureteroscope and gastroscope, respectively. This maneuver exposed the hilar elements, such as the renal vein, renal artery and urinary excretory structure. The renal vessels were then individualized and completely dissected from the surrounding tissues using instruments introduced through the 2 endoscopes, which worked in coordinated fashion.

After the renal artery and vein were completely dissected and circumferentially individualized the ureteroscope was removed from the peritoneal cavity. Subsequently 5 mm ultrasonic scissors were introduced into the peritoneal cavity through the transvesical over tube and guided to the renal hilum using the gastroscopic image. The artery was positioned between the blades of the ultrasonic scissors and divided using level 1 for maximum coagulation. The renal vein was divided in a similar procedure. In 2 pigs the renal vessels were clipped before division by the ultrasonic scissors. It is worth mention that the renal vessels were divided using 5 mm transvesical instruments, which were used under gastroscope guidance. When the renal hilum was completely free, we completed kidney dissection by isolating and mobilizing the upper pole using transvesical ultrasonic scissors or the needle knife, always under gastroscope guidance. Finally, we divided the ureter by half of its trajectory and the kidney was dragged from its bed in the direction of the stomach, held by an endoscopic snare. However, the kidney was left in the animal since we were not able to extract it with the current instruments.

After removing the organ the hilar renal area was washed and inspected for bleeding. Adjacent organs were evaluated for evidence of laceration and perforation.

RESULTS

Nephrectomy by the combined transgastric and transvesical approach was done in 6 pigs. The procedures involved in the creation of the vesical hole (cystoscopy, bladder mucosal incision, cystotomy and transvesical over tube passage) were performed easily and rapidly, and without complications in all animals. The ureteroscope was introduced in straightforward fashion into the peritoneal cavity and CO_2 insufflation was performed without incident. The ureteroscopic image was particularly valuable for helping the gastroscope operator select the most appropriate point for gastrotomy on the anterior gastric wall (fig. 2). Additionally, the external view of the gastric wall provided by the ureteroscope allowed us to create the gastrotomy while preventing damage to the major gastric vessels and adjacent structures (fig. 2, *B*). In fact, beginning access to the peritoneal cavity through the transvesical approach resulted in no complications during gastric incision and gastroscope entrance into the peritoneal cavity.

From the transgastric and transvesical ports it was possible to easily find the selected kidney for nephrectomy

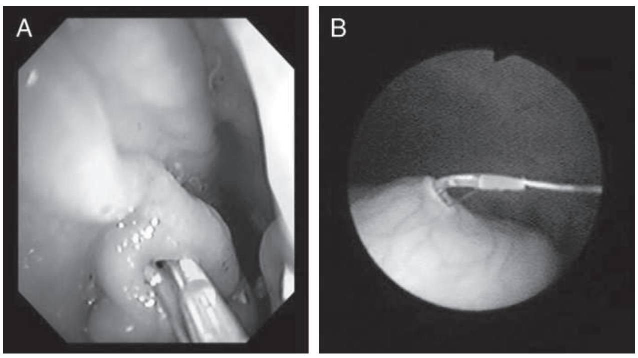

FIG. 2. Gastrotomy creation with papillotomy knife. *A*, gastroscopic image shows internal view. *B*, ureteroscopic image shows external view.

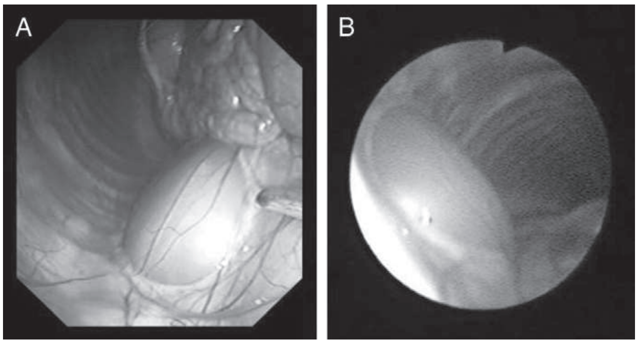

FIG. 3. Renal identification before starting dissection. *A*, gastroscopic image. *B*, ureteroscopic image.

(fig. 3). It should be stressed that the gastroscope was used most of the time in retroflexion. In fact, the kidney was more easily visualized by the gastroscope in the retroflexion position, directing its tip toward the upper quadrant. This allowed us to work with the gastroscope in a stable position.

Further procedures in the performance of nephrectomy were done using coordinated movements of the gastroscope and ureteroscope operators, which increased during the experimental protocol. Creation of a peritoneal window in the lower pole of the kidney and subsequent dissection to expose the renal hilum were accomplished in all animals in a rapid and safe way (fig. 4). These procedures were done most of the time by the gastroscope operator, whereas the ureteroscope operator grasped the peritoneum. Maneuvers to dissect and isolate the hilar vessels were done using gastroscope or ureteroscope instruments, always in coordinated movements (fig. 5). Although it was time-consuming, vessel isolation was reasonably accomplished without hemorrhage in all animals.

To promote renal vessel ligation we always used the same sequence, characterized by removal of the ureteroscope and followed by the introduction of ultrasonic scissors into the peritoneal cavity through the transvesical over tube. Transvesical instrument exchange was always guided by the gastroscopic image (fig. 6). In the first 2 animals ligation of the artery and vein with the ultrasonic scissors was efficient with no evidence of hemorrhage (figs. 7 and 8). In animals 3 and 4 ultrasonic ligation of the renal artery was insufficient, causing mild hemorrhage that significantly blurred the view of renal hilar structures. Although in these cases hemorrhage could be safely controlled with gastroscope instru-

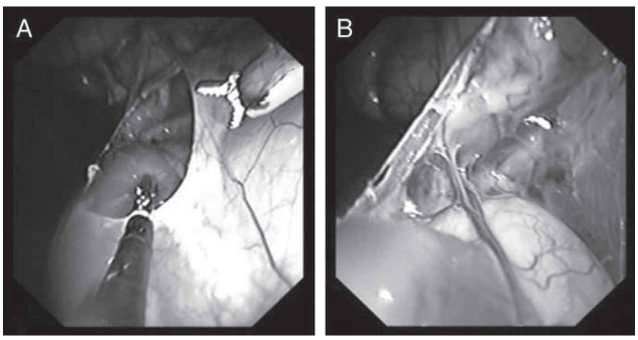

FIG. 4. Creation of peritoneal window for hilar approach. *A*, opening peritoneum. *B*, visualizing hilar elements.

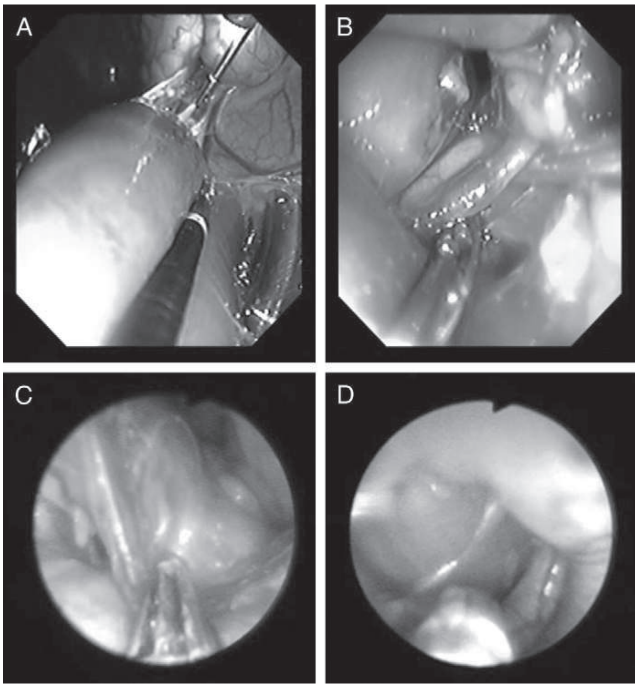

FIG. 5. Renal vessel dissection. *A*, gastroscopic view of renal vein. *B*, gastroscopic view of renal artery. *C*, ureteroscopic view of renal artery. *D*, ureteroscopic view of renal vein.

ments, such as grasping forceps followed by ultrasonic cautery reapplication, in the last 2 animals we successfully applied endoscopy clips before ultrasonic ligation to increase the safety of vessel ligation. Clip application was easy and

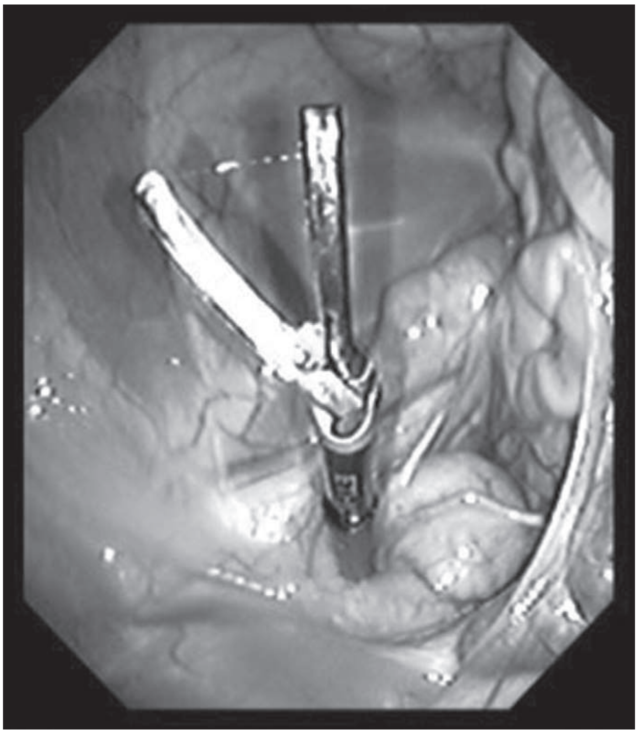

FIG. 6. Gastroscopic view of entrance of ultrasonic scissors into abdomen by transvesical port.

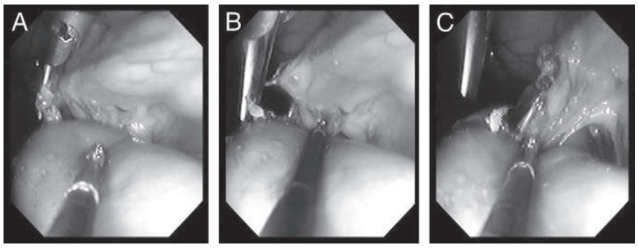

FIG. 7. Gastroscopic image reveals renal artery ultrasonic ligation. *A*, starting ligation. *B*, finishing ligation. *C*, completed ligation.

this approach was particularly successful with hemorrhage in none of these cases.

After vessel ligation ureteral dissection and section were easily accomplished in all animals (fig. 9). The kidney was easily released by sectioning the peritoneum from the upper renal pole and posterior perirenal tissue. For these procedures we used gastroscope cautery or transvesical ultrasonic scissors. The kidney was then mobilized from the renal bed, held with a gastroscopic snare and pulled to the stomach (fig. 10).

Nephrectomy was performed under pressure controlled CO_2 pneumoperitoneum. However, it should be emphasized that most of the time the surgical procedure was performed under a low CO_2 pressure of around 3 mm Hg. In fact, pneumoperitoneal pressure was increased up to 12 mm Hg only during gastric perforation and exchange of the transvesical surgical instrument.

Median time for the overall procedure, including establishment of the transvesical and transgastric port, was around 120 minutes (range 90 to 150). Procedure time decreased with experience.

All animals were sacrificed at the end of the nephrectomy procedure, immediately after surgery. Necropsy did not reveal any damage to the abdominal viscera that was related to transgastric and transvesical access to the peritoneal cavity. It was possible to confirm nephrectomy and perfect ligation of the renal vessels.

DISCUSSION

The current study confirms that nephrectomy is feasible exclusively by NOTES. Moreover, the combined transgastric and transvesical approach was particularly useful for complete renal manipulation. Thus, renal intervention might be included in the list of potential clinical indications for NOTES.

This study describes a revolutionary surgical approach that is being used for an increasing number of procedures, such as

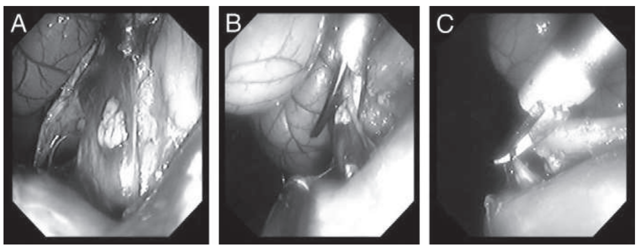

FIG. 8. Gastroscopic image demonstrates renal vein ultrasonic ligation. *A*, dissected vein. *B*, starting ligation. *C*, finishing ligation.

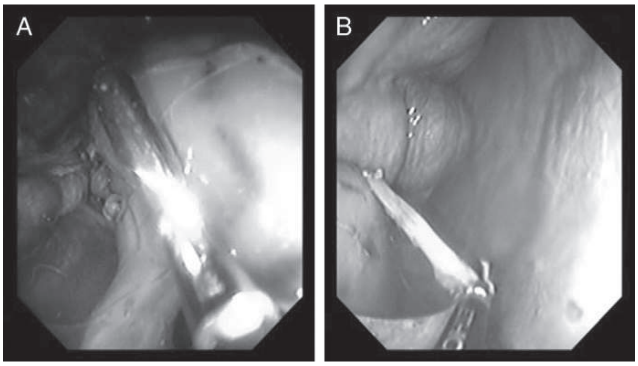

FIG. 9. *A*, individualized ureter. *B*, ureteral ligation

fallopian tube ligation, cholecystectomy, gastrojejunostomy, partial hysterectomy, oophorectomy and splenectomy essentially via the transgastric route.[11–17] In fact, there are several theoretical advantages to NOTES. 1) There are no abdominal incisions and, therefore, abdominal wound infections and incisional hernias are avoided, possibly resulting in less pain and certainly in a better cosmetic effect. 2) There may be potential advantages of a more rapid recovery, fewer adhesions and less postoperative ileus. 3) The natural orifice approach to the peritoneal cavity may be the ideal route in morbidly obese patients.[10]

Believing in the potential benefits of natural orifices approach to abdominal surgery, to our knowledge we were the first group to use a combined transgastric and transvesical approach to perform cholecystectomy, aiming to overcome many limitations that were previously described for the isolated transgastric approach related to anatomy exposure, organ retraction, grasping and limited triangulation.[9] Interestingly the combination of transgastric and transvesical ports was also particularly useful for approaching the kidney, making nephrectomy feasible by NOTES. We used the transvesical port because it is diametrically opposed to the transgastric port and seems to offer additional advantages over transvaginal and transcolonic ports.[18] In fact, although the transvesical port does not support as large instruments as transvaginal and transcolonic ports, it is sterile, available in the 2 genders and seems particularly safe, at least in a porcine model, even when left unclosed. Moreover, the bladder dome offers the most anterior position in the lower abdomen, allowing the introduction of surgical instruments above the bowel loops.[7,19] As proven by Gettman et al,[5] the great advantage of the transvaginal approach is its availability to remove the specimen.

Regarding the surgical technique, after a short learning curve we could open the renal peritoneum and dissect the renal vessels and ureter in a safe way. To open the peritoneum and dissect the hilum the coordination of the gastroscope and ureteroscope operators was vital. In fact, the 2 operators were constantly alternating their intervention on dissection vs retraction procedures. Whereas the ureteroscope had the advantage of being rigid, it had a significant limitation in width and image resolution as well as its fragile instruments. In contrast, the gastroscope had an enormous advantage in width and image quality but its flexibility and unstable platform frequently compromised its intervention. The gastroscope operator dealt with this limitation, working frequently in retroflexion with the gastroscope loop supported on the abdominal walls. With this approach we could dissect the right or left kidney in a similar way. However, it might be emphasized that in pigs the 2 kidneys are not hidden by the colon. In fact, predicting translation into humans, we should not neglect that the colon loop might complicate any renal approach by NOTES.

Regarding vessel ligation, we refused the idea of using an endoscopic loop to ligate the renal vein and artery simultaneously, as others described for splenectomy.[17] We chose to individualize each vessel, which we reasonably accomplished in the majority of cases, ligating them individually with ultrasonic scissors. Ultrasonic ligation was sufficient for most vessels but in 2 animals we observed mild hemorrhage after ultrasonic ligation. In this sequence we successfully applied surgical clips in some animals before ultrasonic ligation. The ureter was also easily dissected and ligated in all cases. After complete kidney release we used an endoscopic snare to hold up the organ and pull it out to the stomach.

During our experiments we realized that most of the time we could work safely with a low CO_2 pressure of approximately 3 mm Hg. We have 2 major explanations for this finding. 1) The entrance of the instruments into the abdomen is parallel to the abdominal wall. Thus, we do not need significant pneumoperitoneum because the instruments use the abdominal wall as a fulcrum when mobilized. 2) The close-up properties of endoscopic instruments, particularly the gastroscope, might be particularly relevant because, if confirmed in posterior experiments, it could mean that the surgical stress of NOTES procedures might be significantly decreased compared with that of laparoscopy. In fact, most surgical laparoscopic stress is related to CO_2 pressure.[20]

A major limitation of the current technique is related to our inability to safely close the gastrotomy. In fact, a critical element of any transgastric procedure is the ability to securely close the gastrotomy site that is required for endoscope passage and specimen removal. It is generally considered that an appreciable increase in patient morbidity from postoperative gastric leaks would expunge any patient advantage of the transgastric approach. For NOTES to achieve widespread adoption gastrotomy closure must be completely reliable. In this regard there are currently several endoscopic suturing devices in development.[21] Because we do not have available at our laboratory a reliable device to close the gastrotomy, we did not enlarge the gastrotomy to pull the specimen into the stomach. To promote its extraction we

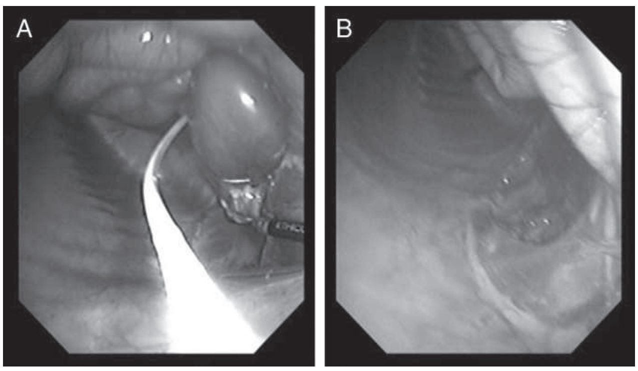

FIG. 10. Completed nephrectomy. *A*, gastroscopic snare drags released kidney. *B*, renal bed after kidney removal.

predicted that it would be removed after its division or morcellation. Thus, we decided to sacrifice all animals after nephrectomy and necropsy revealed that the renal vessels were completely sealed.

A common drawback of the NOTES approach is its limited capability to deal with perioperative complications. Although we were able to control mild hemorrhage with current commercial instruments, we believe that new instruments and devices are needed to increase our confidence in NOTES to perform complex intra-abdominal surgical procedures. Current ureteroscopes are highly developed for diagnostic and limited therapeutic tasks in the urinary tract but they are far from the ideal design to be used in NOTES. They have several limitations that limit their capabilities. 1) The image quality of the ureteroscope is not similar to that of the gastroscope or laparoscope and light intensity is also sometimes inadequate. 2) Ureteroscopes usually have a diameter of between 3.3 and 4.3 mm with 1 or 2 working channels of 4.2 Fr and 6.6 Fr, respectively, which limits the size of instruments. The endoscope shaft should be 5 mm and it should contain a larger channel to introduce other instruments with better efficiency. 3) Although the current rigid ureteroscope has some advantage for NOTES, such as allowing vigorous organ retraction for exposure, its rigidity might be a limitation to achieve retroperitoneum and other organs that are not in the axis of the bladder dome. Moreover, the tip of the ureteroscope should have flexibility and the ability to maneuver in all planes, allowing better tissue manipulation. The ideal device should allow complete rigidity for insertion and positioning with subsequent rigidity of the shaft, allowing traction/counter traction and continued flexibility of the tip, which should free the surgeon hands to manipulate different organs and tissues. 4) We should emphasize that the ultrasonic shears and even the clips that we used in this study for hilar ligation are not consensually approved for human purposes.

Although these concepts of NOTES could seem futuristic, we believe that guidelines for NOTES have already been established. Moreover, robotics and magnetic positioning technology can provide additional input for NOTES.[22] The feasibility of nephrectomy by NOTES appears in our understanding as the extreme of a large spectrum of renal procedures that can potentially be done by NOTES in the near future. However, we might consider that much study is still needed to refine techniques, verify safety and document efficacy before translation into humans to minimize unexpected complications.

CONCLUSIONS

Right and left nephrectomy using NOTES was feasible in a porcine model. Our study also demonstrates the limitations of the standard devices since we could not reliably achieve gastrotomy closure and remove the specimen. This study provides encouragement to further innovative programs to create devices designed to advance the safety of NOTES.

ACKNOWLEDGMENTS

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Abbreviations and Acronyms

NOTES = natural orifice transluminal endoscopic surgery

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Chapter 6.
In-vivo Assessment of Gastrotomy Closure & Transgastric Varicocelectomy

***In-vivo* Assessment of Gastrotomy Closure by**
Over-the-Scope-Clips in an Experimental Model for Varicocelectomy

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Macedo G, Correia-Pinto J.

Gastrointest Endosc 2009 Jul 30. (Epub ahead of print).

ORIGINAL ARTICLE

In vivo assessment of gastrotomy closure with over-the-scope clips in an experimental model for varicocelectomy (with video)

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Background: Gastrotomy closure remains the major limiting factor for human translation of transgastric surgery; the over-the-scope clip (OTSC) system was proposed as a possibility for this purpose. Transgastric access is good for a pelvic approach, making varicocelectomy a possible indication for natural orifice transluminal endoscopic surgery (NOTES).

Objective: To evaluate the reliability of the OTSC system in vivo after transgastric testicular vessel ligation (varicocelectomy model).

Design: There were 3 experimental groups (5 animals in each): groups 1 and 3, gastrotomy dilation up to 18 mm, surgery was performed with a double-channel endoscope; group 2, gastrotomy dilation up to 13 mm, surgery was performed with a single-channel endoscope.

Setting: Surgical Sciences Research Domain, Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Braga, Portugal.

Interventions: Bilateral testicular vessel ligation by transgastric access. Gastrotomy closed with the largest version of OTSC system (12 mm): a single clip in groups 1 and 2, and 2 clips in group 3. Animals were monitored for 2 weeks, killed, and submitted for necropsy.

Main Outcome Measurements: Adequacy of closure and healing after the use of the OTSC system. Statistical analysis.

Results: Vessel ligation was easily achieved in all groups. Although differences in the complication rate did not reach statistical significance ($P = .099$), there was a clear tendency for a better prognosis in groups 2 and 3 than group 1. In fact, only 2 animals from group 1 had complications related to incomplete gastrotomy closure.

Limitations: Small number of animals per group; nonrandomized study.

Conclusions: The OTSC system was shown to be easy and efficient for gastrotomy closure in a survival experimental model of varicocelectomy, when correctly matching the gastrotomy size with the clip size and/or number. (Gastrointest Endosc 2009;■:■-■.)

Envisioning the potential benefits of natural orifice transluminal endoscopic surgery (NOTES), many investigators tested the feasibility of NOTES in the peritoneal and even in the thoracic cavities.[1,2] From all previous experimental work, the transgastric approach was shown to be particularly applicable for performing surgical procedures in the pelvis.[3,4]

Simultaneously, analyses by leaders in the fields of surgery and endoscopy revealed 3 fundamental challenges and barriers to the safe implementation of NOTES: access creation, prevention of infection, and visceral closure.[5] Gastrotomy creation could be achieved with PEG-like,[6] hybrid or transvisceral combined[7-9] approaches, and the risk of contamination seems a matter of adequate endoluminal disinfection and intravenously administered antibiotics, but the solution to achieving secure closure of the gastric

Abbreviations: NOTES, natural orifice transluminal endoscopic surgery; OTSC, over-the-scope clip.

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defect remains more difficult, and development of endoscopic closing devices continues to be a prime area of research and testing.[10] Indeed, this aspect seems to be the most limiting factor for human translation of transgastric procedures and likely justifies the still-scarce number of reports of successful NOTES in humans.[11,12]

Regarding closure techniques, several methods have been proposed, including conventional endoscopic clips,[1] an over-the-scope clip (OTSC) system,[13] septal occluders,[14] T-tags,[15] and T-bars[16] for tissue opposing, as well as more complex suturing devices such as the Eagle Claw VII (Olympus Optical Co, Ltd, Tokyo, Japan),[17] NDO Plicator (NDO Surgical Inc, Mansfield, Mass),[18] USGI Endosurgical Operating System (San Clemente, Calif),[19] and linear endoscopic staplers.[20] Moreover, special techniques in gastrotomy creation and closure, as described by Sumiyama et al[21] who used submucosal endoscopy with an offset exit gastrotomy or by Sporn et al,[22] who used a PEG technique combined with gastropexy, have been suggested. However, most of these devices and techniques still have limitations that need improving, and most of them are too complex to apply or could not prove their effectiveness in survival studies.

The OTSC system has a simple method for application, and it was already approved for clinical use in cases of bleeding and iatrogenic lesions of the digestive tract.[23] An enlarged version of the OTSC system was evaluated for the use in NOTES with promising results in a nonsurvival study,[24] highlighting the need for such studies.

Aiming to test the efficacy and reliability of the OTSC system in vivo for gastric closure, we used the OTSC system in a survival porcine model after performing a simple pelvic procedure such as bilateral testicular vessel ligation.

Capsule Summary

What is already known on this topic

- Reliably safe transgastric access could make varicocelectomy a possible indication for natural orifice transluminal endoscopic surgery.

What this study adds to our knowledge

- In a study of bilateral testicular vessel ligation by transgastric access, an over-the-scope system allowed easy and efficient gastrotomy closure in a porcine model when the gastrotomy dimension correlated with the clip size.

MATERIALS AND METHODS

Study design

Male pigs (*Sus scrofus domesticus*) weighing 40 to 45 kg were used to perform a simple pelvic procedure by NOTES, a transgastric bilateral testicular vessel ligation. After an initial learning curve, the results of which results are not reported here, 15 animals were divided in 3 groups: group 1, 5 pigs, all procedures (gastrotomy and surgery) were performed by using a double-channel gastroscope and at the end, a single 12-mm OTSC was applied by using the same endoscope; group 2, 5 pigs, gastrotomy and surgery were performed with a standard single-channel gastroscope and at the end, a single 12-mm OTSC was applied by using a double-channel endoscope; group 3, 5 pigs, all procedures (gastrotomy and surgery) were performed with a double-channel gastroscope and at the end, two 12-mm OTSCs were applied by using the same endoscope. The animals in all groups were monitored with a 15-day survival follow-up. This study was approved by ethics review board of Minho University (Braga, Portugal).

Pig preparation

The animals were fed liquids for 3 days and received no food and water for 8 hours before the surgical intervention. The stomach was lavaged with instilled water and aspirated through the gastroscope until free of solid particles. Subsequently, it was decompressed and a cefazolin solution (1 g in 200 mL of saline solution) was instilled. The antibiotic solution was left in the stomach for 10 minutes before also being aspirated. All procedures were performed with the pigs under general anesthesia with endotracheal intubation and mechanical ventilation, as described in previous studies.[8,9]

Surgical technique

Transgastric access. A double-channel endoscope (G28/34; Karl Storz GmbH & Co KG, Tuttlingen, Germany) was advanced into the stomach. After stomach preparation, the preferred gastrotomy site was chosen on the anterior wall by transillumination and external palpation. After gastric wall incision with a needle-knife, puncture dilation was performed with an 18-mm through-the-scope balloon (5837 Microvasive; Boston Scientific Corp, Natick, Mass) for the double-channel gastroscope passage in groups 1 and 3, and with a 13-mm through-the-scope balloon (5836 Microvasive; Boston Scientific Corp) for passage of a regular single-channel gastroscope (G28; Karl Storz GmbH & Co KG) in group 2. Then on balloon semideflection, the gastroscope was pushed forward into the peritoneal cavity and directed to the pelvic cavity.

Testicular vessel ligation. The animal was placed in a slight head-down position (Trendelenburg up to 30 degrees), and the gastroscope was positioned for anteroinferior abdominal wall exploration. Once the internal inguinal ring and the spermatic cord were identified, the gonadal vessels were approached, sparing the vas deferens. In groups 1 and 3, two instruments were allowed: a grasping forceps and a coagulation grasper. By using these instruments, it was possible to grasp and cut the parietal peritoneum overlying the testicular vessels, high above the internal inguinal ring, to create a window to reach and mobilize the vessels. When isolation was completed, the

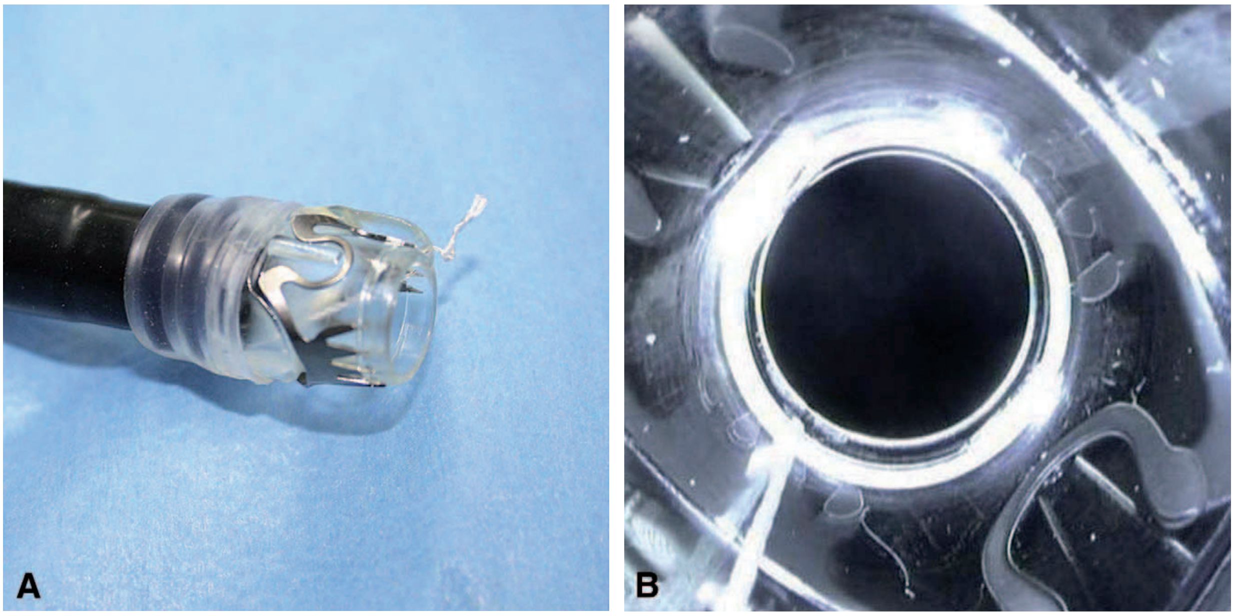

Figure 1. OTSC system mounted on the tip of the gastroscope: **A,** External view. **B,** Restricted image provided by the gastroscope with the OTSC system mounted.

coagulation grasper was used for a soft coagulation appliance in 2 points of the vessel segment and then cut in the middle for section. In group 2, only 1 instrument could be used at a time, and almost all the procedure was done by using the coagulation grasper, although a less careful dissection had been achieved. In all groups, the procedure was repeated on the contralateral side. The CO_2 pneumoperitoneum was controlled and maintained up to a maximum of 12 mm Hg with a Veress needle.

Gastrotomy closure

At the conclusion of the intra-abdominal procedure, the endoscope was withdrawn. The OTSC system (Ovesco Endoscopy GmbH, Tubingen, Germany) was mounted on the tip of the double-channel gastroscope, charged with a 12-mm clip (Fig. 1), and inserted into the stomach. After visualization of the transgastric hole, in groups 1 and 2, a single clip was applied according to the manufacturer's instructions, after centering the clip over the gastrotomy. In group 3, the first clip was slightly deviated for one of the extremities of the gastrotomy, whereas the second was centered on the other extremity of the gastrotomy and involved part of the first clip (Video 1, available online at www.giejournal.org). Once applied in all groups, the clips were inspected and the tightness of the closure was confirmed by means of air inflation and the ability to maintain organ distention.

Postoperative care

At the end of the surgical intervention, all animals received 1.2 g amoxicillin and clavulanic acid intravenously. A liquid diet was resumed 8 hours after surgery and a regular diet 2 days later. The animals were closely monitored for any signs of postoperative complications, distress, behavior changes, anorexia, or weight loss. After the follow-up period, the animals were killed and necropsy was performed to check the healing of the gastric wall incision and signs of intraperitoneal complications.

Statistical analysis

Continuous variables are presented as mean ± standard deviation. In the experimental groups the total operative time of the procedures passed the kolmogorov-smirnov normality test; thus, this parameter was compared with the one-way ANOVA analysis. The postoperative and necropsy findings (rate of postoperative complications related to incomplete gastrotomy closure, gastrotomy position, persistence of clip on site, and presence of omentum mesh) were compared by using χ^2 analysis of contingency because there were more than 2 groups. However, once 20% of the expected values in contingency tables are less than 5, the power of the performed test is below the desired power of 0.8. Statistical significance was set at $P < .05$.

RESULTS

The complete cleansing of the pigs, stomachs was difficult, even with a liquid diet for an easier emptying. The transgastric port creation had no significant complications besides some accidental injuries to the anterior abdominal wall during the needle-knife procedure, but no lesions on adjacent organs occurred. Pelvic assessment, vessel identification, and position adjustments were easily obtained. The Trendelenburg position and a slide left or right rotation favored the displacement of intestinal loops,

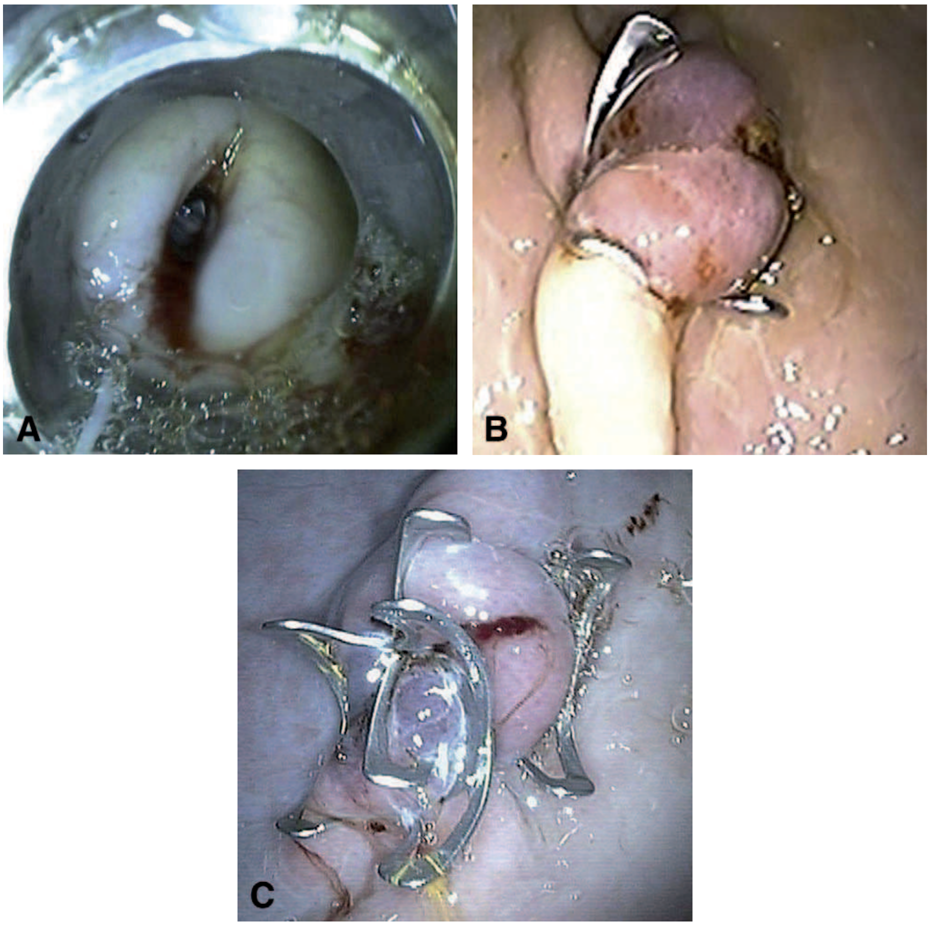

Figure 2. Gastrotomy closure. **A,** OTSC system mounted on the tip of the gastroscope, already in the stomach and having the gastrotomy on the image center. **B,** One clip positioned and the defect closed (groups 1 and 2). **C,** Two clips positioned and the defect closed (group 3).

allowing good anatomical exposure. In groups 1 and 3, the surgical procedure was more elegant than group 2, but we could isolate and safely ligate the vessels easily in all groups. In fact, no adverse events or bleeding complications occurred.

We found the OTSC system easy and intuitive. The most tedious step was the need for gastroscope removal and loading. Before clip release, a mesh of omentum was sometimes pulled into the stomach during gastroscope withdrawn or suction, and its endogastric portion was snared and cut after the clip application (this occurred in 1 pig in group 1, 2 pigs in group 2, and 1 pig in group 3). Immediately after gastrotomy closure, all clips seemed well positioned, and the stomachs were able to maintain distention on air inflation (Fig. 2).

The mean time for the overall procedure, including transgastric port establishment, bilateral testicular vessel ligation, and gastrotomy closure was 64.0 ± 9.4, 53.8 ± 5.5, and 59.2 ± 7.7 minutes for groups 1, 2, and 3, respectively ($P = .18$).

Postoperative follow-up and necropsy results are shown in Table 1. Although comparison of complication rates (related to incomplete gastrotomy closure) among the 3 groups did not reach statistical significance ($P = .099$), there was a clear tendency for a better outcome in groups 2 and 3 than group 1. In fact, in group 1, one animal died within the first 24 hours after the procedure and another experienced anorexia and progressive prostration during recovery and was killed 12 days after surgery (both had evidence of incomplete gastrotomy closure), whereas the remaining animals had an uneventful recovery. In groups 2 and 3, the postoperative recovery and the survival period progressed without adverse events related to surgery. In fact, all the pigs ate heartily and gained weight with no evidence of infection during the 2 weeks after the procedure. All animals that completed the study follow-up period had complete healing of the gastrotomy and no evidence of intra-abdominal abscesses or adhesions (Fig. 3), whereas no significant differences were identified among the groups when comparing gastrotomy position ($P = .74$), persistence of clip on site ($P = .12$), and the presence of omentum mesh on the external side of the stomach ($P = .74$) at necropsy analysis.

TABLE 1. Postoperative follow-up and necropsy data

	Survival follow-up	Necropsy
Group 1 (gastrotomy dilation 18 mm, 1 clip applied)		
1	Dead 24 h later	Leakage Anterior gastrotomy Clip on site; incomplete closure
2	Good recovery	No intra-abdominal complications Posterior gastrotomy No clip; defect healed
3	Progressive clinical deterioration; killed at 12 d	Peritonitis Anterior gastrotomy Clip on site; incomplete closure
4	Good recovery	No intra-abdominal complications Anterior gastrotomy No clip; defect healed Mesh of omentum on external side
5	Good recovery	No intra-abdominal complications Posterior gastrotomy Clip on site; complete closure
Group 2 (gastrotomy dilation 13 mm; 1 clip applied)		
1	Good recovery	No intra-abdominal complications Anterior gastrotomy No clip; defect healed
2	Good recovery	No intra-abdominal complications Anterior gastrotomy No clip; defect healed Mesh of omentum on external side
3	Good recovery	No intra-abdominal complications Posterior gastrotomy No clip; defect healed Mesh of omentum on external side
4	Good recovery	No intra-abdominal complications Posterior gastrotomy Clip on site; complete closure
5	Good recovery	No intra-abdominal complications Anterior gastrotomy Clip on site; complete closure
Group 3 (gastrotomy dilation 18 mm; 2 clips applied)		
1	Good recovery	No intra-abdominal complications Anterior gastrotomy Clips on site; complete closure

(*continued on next page*)

TABLE 1 (*continued*)

	Survival follow-up	Necropsy
2	Good recovery	No intra-abdominal complications Anterior gastrotomy Clips on site; complete closure Mesh of omentum on external side
3	Good recovery	No intra-abdominal complications Anterior gastrotomy Clips on site; complete closure Mesh of omentum on external side
4	Good recovery	No intra-abdominal complications Posterior gastrotomy Clips on site; complete closure
5	Good recovery	No intra-abdominal complications Anterior gastrotomy Clips on site; complete closure

DISCUSSION

We assessed the efficacy and reliability of the OTSC system in vivo for gastric closure in a survival porcine model after bilateral testicular vessel ligation, transgastric varicocelectomy, a simple intra-abdominal surgical procedure that would work as a novel indication for NOTES.

In this study, we used the male pig as an experimental model. This should be taken into account in survival studies such as this one because pig studies are likely the extreme of luminal contamination and peritoneal dissemination risk. In fact, we found it sometimes difficult to obtain a clean stomach in these animals. However, the human stomach is usually clean after some hours of fasting, and some studies suggest that transgastric endoscopic peritoneoscopy does not require stomach decontamination in humans.[25] Other important issues are the safety of gastrotomy creation and the stomach anatomy. Several transgastric access procedures have been described,[1-4,6,9,12] but there is a common step in almost all descriptions, the blind use of a needle-knife with cautery that is highly risky for adjacent organs, and this uncertainty is not acceptable for human application. In our study, we did have some anterior abdominal wall injuries. Regarding the optimal location points for gastrotomy, many authors suggest the anterior gastric wall of the corpus or antrum as the preferred location.[26] This is not always accomplished in pigs because of easy gastric rotation, and in our study, gastrotomy location on the posterior gastric wall was not an uncommon finding.

More crucial and likely the most important step for human translation of NOTES is the method used to achieve safe closure of the gastric defect. Among the current methods,[1,13-22,26,27] the OTSC system seemed to us to be the easiest to apply when a single transgastric port is used for simple procedures. The OTSC system efficacy for NOTES for gastrotomy closure had only been tested in a nonsurvival animal study, and although the gastrotomy lesions could primarily be closed, half of the animals revealed that adaptation of the wound margins was not completely airtight under maximum inflation of the stomach.[24] Believing in the concept of the OTSC system, we designed this protocol with 3 groups in which we varied the gastrotomy size and the number of clips applied to test their in vivo efficacy.

Our experience with OTSC in this study reveals some advantages and disadvantages. We had confirmed its simplicity and intuitive and easy application. However, when mounted over the scope, the cap narrows the field of vision and enlarges the gastroscope tip dimension (up to 18 mm), increasing the risk of esophageal trauma. We think that these aspects were improved with the new transparent and less traumatic cap currently available. Another concern is the risk of adjacent structure involvement during suction. Although bowel loop aspiration never occurred in our protocol, the aspiration of omentum into the stomach through the opening occurred sometimes. We dealt with this by coagulating and cutting it with a snare after the clip application, and there were no related problems. This could even work as an advantage to enhance gastrotomy healing because it is well-known that a patch of omentum could increase the security of bowel perforation repair. Another relevant conclusion drawn from this study is that the stomach's ability to maintain distention with air inflation immediately after closure is not a totally reliable

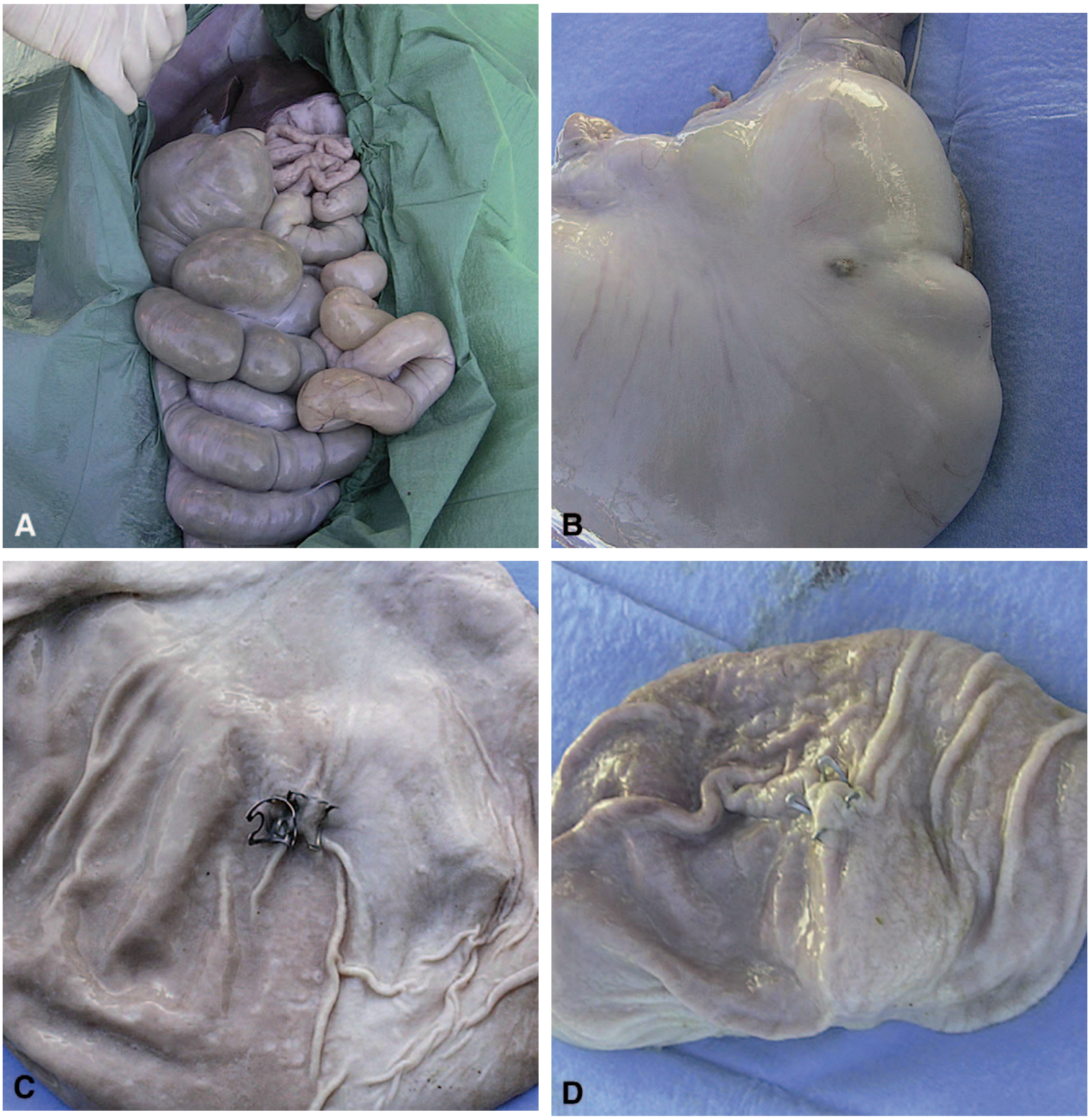

Figure 3. Necropsy findings. **A,** Overall abdominopelvic view. **B,** Gastric external view of the healed gastrotomy. **C,** Internal gastric wall with 2 clips in position. **D,** Internal gastric wall with 1 clip in position. **E,** Internal gastric wall showing the healed defect without clip.

method to confirm good gastrotomy sealing. In fact, although all animals could maintain air distention in the stomach immediately after clip application, in group 1, two animals presented complications related to incomplete gastrotomy closure. Our explanation for this is that acute gastric sealing could be obtained in those animals because of mucosa congestion and/or edema that with time regressed, exposing a leak.

The results of our study validate the potential applicability of the OTSC system in vivo, but they also stress the need to find the perfect match of clip and gastrotomy size. Usually for passing a double-channel gastroscope, we used balloon dilation up to 18 mm; the results for group 1 of 2 incomplete closures in 5 pigs raise some concerns regarding the safety of this clip for this size opening. In group 2, when we dilated just up to 13 mm for single-channel gastroscope passage, the results were 100% successful. Although there are 2 sizes of clips available, each one adapting to the 2 regular diameters of flexible endoscopes, the message here is that it is safer to apply a clip that is larger than the endoscope used

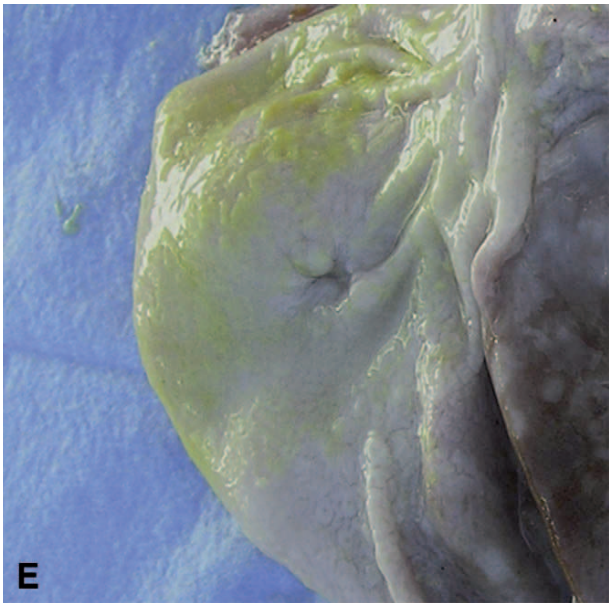

Figure 3 (*continued*)

for transgastric surgery, seeking a better match between the clip and gastrotomy size. Of course a problem still remains: how to close larger openings, mainly when large multitasking platforms are used? Attempting to answer this question, we used a third experimental group with the largest gastrotomy (similar to group 1), in which we applied 2 clips instead of only 1 clip. Surprisingly, we found it easy to apply a second clip even if it is released partially overlapping the first clip. Follow-up of the pigs in group 3 revealed no complications, suggesting that 2 clips could be a reasonable solution for larger gastrotomies. We believe that for simple procedures, as used in our study, thinner endoscopes would be sufficient, and a single-clip adequate to close the gastrotomy. These findings might have implications for other more complex procedures in which a combined hybrid approach might be a smooth transition for pure NOTES while new endoscopes and devices are being developed.

We selected a simple and effective surgical procedure, and the anatomical exposure of the pelvic excavation and anteroinferior abdominal wall for testicular vessel ligation was excellent, with the help of some external adjustments such as use of the Trendelenburg position. Testicular vessel ligation was intentionally chosen because it mimics a current procedure performed in males, varicocelectomy. The term varicocele defines an abnormal tortuosity and dilation of the testicular veins in the pampiniform plexus that has an overall incidence of approximately 10% to 15%, and there is a clear association among varicocele, infertility, and testicular growth arrest. It is also known that varicocelectomy can reverse growth arrest in adolescents with varicocele, and all those aspects support an early intervention in selected cases.[28] Accepting this new era of transforming surgery in an even more minimally invasive field, we tested successfully that varicocelectomy, when using a modified Palomo approach, could became a novel and good indication for NOTES.

In conclusion, the OTSC system was easy to apply and efficient in gastrotomy closure in an experimental survival model of varicocelectomy when correctly matching the gastrotomy size and clip size and/or number. This study encourages further research to make simple pelvic procedures performed by the transgastric approach safe in humans.

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Chapter 7. Peroral Esophageal Segmentectomy & Anastomosis

Peroral Esophageal Segmentectomy and Anastomosis with Single Transthoracic Trocar Assistance: A Step Forward in Thoracic NOTES

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Abstract: Background: Transesophageal NOTES (Natural Orifice Transluminal Endoscopic Surgery) approach has been proposed for thoracic and mediastinal access. Similarly to transgastric surgery, serious limitations remain related with esophagotomy creation and safety closure. Hybrid approach in thoracic NOTES could work as an intermediate step before pure transesophageal NOTES.
Objective: To assess the benefit of hybrid thoracic NOTES performing a complete peroral esophageal anastomosis, after segmental esophagectomy with assistance of a single transthoracic port.
Design: Two protocols were carried out to perform esophago-esophageal anastomosis: i) ex-vivo using a phantom model (5 porcine esophagus); ii) in-vivo after esophageal mobilization, and segmental esophagectomy (5 anesthetized pigs).
Setting: Surgical Sciences Research Domain, Life and Health Sciences Research Institute, School of Health Sciences, University of Minho, Portugal.
Patients: N/A.
Interventions: A forward viewing double-channel endoscope and a transthoracic telescope with working-channel were coordinated in order to create a complete, single-layer and end-to-end esophageal anastomosis ex-vivo as well as in-vivo after mobilization and segmental resection of esophagus (4cm).
Main Outcome Measurements: Assessment of feasibility and anastomosis quality by inside and outside: patency, incorporation of mucosa in all stitches and leak tests.
Results: Anastomosis was always achieved in both protocols. All anastomosis were patent allowing distal passage of the endoscope with mucosa incorporation. In in-vivo experiments leak was detected in three animals that were corrected with additional stitching.
Limitations: Non-survival study.
Conclusions: Peroral esophageal anastomosis with single transthoracic trocar assistance is feasible, which represents a step forward in thoracic NOTES.

***A. Cover Page (Title, all author names, affiliations, and degrees, corresp author contact information)**

PERORAL ESOPHAGEAL SEGMENTECTOMY AND ANASTOMOSIS WITH SINGLE TRANSTHORACIC TROCAR ASSISTANCE: A STEP FORWARD IN THORACIC N.O.T.E.S.

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Runninghead: Peroral esophageal anastomosis.

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2. Manuscript Text

PERORAL ESOPHAGEAL SEGMENTECTOMY AND ANASTOMOSIS WITH SINGLE TRANSTHORACIC TROCAR ASSISTANCE: A STEP FORWARD IN THORACIC NOTES.

Background: Transesophageal NOTES (Natural Orifice Transluminal Endoscopic Surgery) approach has been proposed for thoracic and mediastinal access. Similarly to transgastric surgery, serious limitations remain related with esophagotomy creation and safety closure. Hybrid approach in thoracic NOTES could work as an intermediate step before pure transesophageal NOTES.

Objective: To assess the benefit of hybrid thoracic NOTES performing a complete peroral esophageal anastomosis, after segmental esophagectomy with assistance of a single transthoracic port**.**

Design: Two protocols were carried out to perform esophago-esophageal anastomosis: i) *ex-vivo* using a phantom model (5 porcine esophagus); ii) *in-vivo* after esophageal mobilization, and segmental esophagectomy (5 anesthetized pigs).

Setting: Surgical Sciences Research Domain, Life and Health Sciences Research Institute, School of Health Sciences, University of Minho, Portugal.

Patients: N/A.

Interventions: A forward viewing double-channel endoscope and a transthoracic telescope with working-channel were coordinated in order to create a complete, single-layer and end-to-end esophageal anastomosis *ex-vivo* as well as *in-vivo* after mobilization and segmental resection of esophagus (4cm).

Main Outcome Measurements: Assessment of feasibility and anastomosis quality by inside and outside: patency, incorporation of mucosa in all stitches and leak tests.

Results: Anastomosis was always achieved in both protocols. All anastomosis were patent allowing distal passage of the endoscope with mucosa incorporation. In *in-vivo* experiments leak was detected in three animals that were corrected with additional stitching.

Limitations: Non-survival study.

Conclusions: Peroral esophageal anastomosis with single transthoracic trocar assistance is feasible, which represents a step forward in thoracic NOTES.

INTRODUCTION

Minimally invasive esophageal approach is being performed more frequently for both benign and malignant esophageal disease.[1] Since the first thoracoscopic mobilization of the esophagus described by Cuschieri in 1992, different techniques of scopic surgery have been introduced.[2,3] However, it should be emphasized that thoracic incisions even if small are painful.[4]

In the NOTES era,[5,6,7,8] a new approach to the thorax and mediastinum has been proposed - the transesophageal access.[9] Although there are descriptions of transvesical-transdiaphragmatic thoracoscopy[10] and transgastric-transdiaphragmatic pericardial fenestration, the most reasonable reported thoracic access is the transesophageal indeed. By using the esophagus as an entry site into the chest a direct access to the thorax and posterior mediastinum could be reasonably established.[11] In fact, the technical feasibility of transesophageal approach has been described in porcine models for several simple thoracic procedures.[9,11,12,13,14,15,16] Even if the general concept might be appealing, the transesophageal approach seems the one that most stretch the limits even in the NOTES world. It may be highly risky for accessing, whereas mechanical abrasion and trauma of surrounding structures is higher when compared with the other visceral access routes. Moreover, the consequences of an ineffective esophagotomy closure can be devastating for the patient due to the morbid consequences of mediastinitis. In this sequence, the well-known problems of NOTES,[17] such as: safe port creation, infection prevention, tissue manipulation, and mainly the suturing and anastomosis establishment, seem to be even more limiting in the transesophageal approach.

Mirroring what is being done in abdominal surgery where the hybrid became a transitional step for humans, in reducing the number of transabdominal ports and getting natural orifice experience without losing safety,[18,19] we hypothesized that the use of a peroral approach in a hybrid mode can significantly reduce the number of transthoracic ports and its related complications, preserving the surgical safety.

Aiming to eliminate most of the current limitations of transesophageal NOTES, we designed a protocol to carry out peroral esophageal mobilization, segmental esophagectomy and esophago-esophageal anastomosis with assistance of a single-trocar to assess the reliability of this strategy for opening, resection and suturing of the esophagus.

Materials and Methods

Study design

This study was approved by ethical review boards of Minho University (Braga – Portugal). It was divided in two main branches: i) *Ex-vivo* studies - esophago-esophageal anastomoses were carried out inside a phantom model (5 porcine esophagus); ii) *In-vivo* studies - esophageal mobilization, segmental esophagectomy, and esophago-esophageal anastomoses were carried out in anesthetized pigs (5 animals). In all situations were used a forward viewing double-channel gastroscope (G28/34 - Karl Storz GmbH & Co KG, Tuttlingen, Germany) and a transthoracic 10 mm telescope with a 5 mm working channel (26036AA - Karl Storz GmbH & Co KG, Tuttlingen, Germany).

Ex-vivo studies

Phantom model

A three-dimensional structure consisting of synthetic polyurethane foam with an attached PVC container was constructed to simulate the thoracic cavity, and a tube with 20 cm in length was used to reproduce the oropharynx. Esophagus harvested from adult pigs were positioned, fixed and sectioned in its middle segment, creating a gap of 4 cm in length between the ends (Figure 1A).The model had a black, non-transparent removable coverage with an opening on the right side for trocar position (Figure 1B).

Surgical technique

The telescope was inserted into the phantom through a 12mm trocar (Excel port, Ethicon Endo-Surgery, Cincinatti, US), whereas the gastroscope was introduced through the proximal esophagus, and the instruments of both were coordinated to carry out an esophago-esophageal anastomosis. Firstly, a suturing needle with a 3-0 absorbable PDS stitch (Polydioxanone, Ethicon Endo-Surgery, Cincinatti, US) was mounted on a needle-holder (26178KPL - Karl Storz GmbH & Co KG, Tuttlingen, Germany), previously passed through the telescope working channel, and introduced into the phantom. Then, the gastroscope approached the free lower extremity of the esophagus, and grasped it on its posterior wall, including always muscle and mucosa, making proximal traction for the first stitch (inside-out) passage. The needle was then repositioned by the needle-holder for upper extremity approaching, whereas the gastroscope promoted esophageal stumps alignment, and esophageal wall traction for outside-in proximal puncture. The knot-tying was achieved by extracorporeal knot techniques using a knot-pusher (26596D - Karl Storz GmbH & Co KG, Tuttlingen, Germany) under the gastroscope vision. Then a scissors (34410MW - Karl Storz GmbH & Co KG, Tuttlingen, Germany) was introduced through the telescope working channel and the sew edges were cut.

This procedure was repeated until 10 single-layer, interrupted sutures had been completed: the posterior stitches with internal knotting and the latest with external knotting. The duration time of the procedure was recorded. At the end, the gastroscope was used to verify the immediate endoluminal reliability of the anastomoses, confirming that mucosa from both tips was touching each other and identifying possible sites for supplemental stitches.

***In-vivo* studies**

Pig preparation

Male 40-50 Kg pigs (*Sus scrofus domesticus*) were fed liquids for 1 day and restrained from food and water (8 hours) before the surgery. All procedures were performed under general anesthesia with endotracheal intubation and mechanical ventilation, according to previous descriptions.[20,21] Before starting the procedure it was administered 1 mg of intravenous atropine.

Surgical technique

The pig was placed in the prone position. A 12 mm trocar was positioned around the eighth intercostal space in the right posterior axillary line, through which was introduced the telescope, whereas CO_2 insufflation was maintained with a pressure up to 6 mmHg. The gastroscope was advanced throughout an oropharyngeal overtube (US Endoscopy) into the esophagus. Using a scissors through the telescope working channel, the mediastinal pleura overlying the esophagus was opened, preserving the vagus nerve. Under endoluminal traction the proximal third esophagus was dissected, mobilized and freed from its surrounds attachments. Then a 4cm length of esophagus was sectioned, and removed perorally. The gastroscope was re-introduced into the thoracic cavity providing traction and alignment of both esophageal stumps for suturing. The anastomosis creation followed the same steps as described in the *ex-vivo* studies. At the end of the procedure, the gastroscope confirmed the anastomosis patency and the mucosa incorporation in all stitches; the outside telescope checked the reliability of the anastomosis looking for bubbles release under saline while the gastrocope was insufflating air inside the esophagus (air leak test).

Results

E*x-vivo* studies

The designed phantom model was easy to operate and simulated reasonably the *in-vivo* anastomosis steps, despite the lung, other thoracic structures, or even the cardio-respiratory movements were not present.

Besides some initial difficulties, we verified a progressive coordination, making possible the construction of a complete, single-layer and end-to-end esophageal anastomosis in all experiments, with at least 10 interrupted sutures having 5 knots each. The crucial step was always the first stitch. Gastroscope grasping of muscular and mucosal layers of distal stump was easily achieved and useful as it provided positioning, and traction for the needle passage (Figure 2A). Similarly, the gastroscope was useful in exposing the proximal extremity and offering counter-traction. Once the needle crossed both extremities, the gastroscope was also effective in monitoring the knotting. The following stitches were progressively easier to apply (Figure 2B). Entrances of the knot-pusher in the thorax were well monitored by the gastroscope image, allowing recommendations of pressure adjustment, or even knot removal when not correctly performed (Figure 2C). The knots edges were easily cut with the scissors (Figure 2D). As the anastomosis evolved, the benefit of the image provided by the gastroscope was gradually reduced, but the need for support and exposure was also less demanding as the anastomosis was reaching its final. Although the aim was single-layer sutures, involving both mucosa and muscle, we found that mucosa easily disjoint from muscle layer and could be involuntarily missed during needle course; the gastroscope was very useful in monitoring the correct transmural involvement and in better exposure whenever necessary. The mean time for complete anastomosis performance was 65.5 ± 10.9 minutes.

The anastomosis was finally checked by its endoluminal aspect for lumen patency, inter-suturing space and stitch mucosal misplacement, and it was found in a few sutures that some stitches did not include the mucosal layer.

I*n-vivo* studies

The prone approach and the CO_2 insufflation provided good exposure of the intrathoracic esophagus without the need for additional retraction instruments. This and the endoluminal transilumination of the esophagus, allowed a rapid access of the telescope to select the esophageal segment of interest, and the easy opening of the pleura overlying it. With the scissors and the help of slight movements of the endoscope providing esophageal traction, it was possible to perform a safe blunt dissection of the esophagus from its adjacent structures (Video 1). Segmental esophagectomy was done, and the specimen was removed perorally without complications in all cases (Figure 3A and 3B). The subsequent steps related with suturing evolved from same principles of the *ex-vivo* training, and besides some movement interference and some additional caution with adjacent structures, the anastomosis was feasible in all cases and reproducible (Video 2). An interesting aspect of these experiments was that the telescope view was sometimes not enough to realize if the needle position was the most appropriate for a specific suture orientation. However, combining the gastroscope view, it was always possible to correct the needle-holder position. The total mean operative time was 101,8 ± 32,9 minutes, including dissection, segmentectomy and anastomosis.

At the end of the procedure, the anastomosis was checked by inside and outside appearance (Video 3). Externally, the telescope was able to inspect the anastomosis surface over endoluminal transilumination, and small rotations provided by the gastroscope (Figure 3C). By inside, all anastomosis were patent allowing distal passage of the endoscope, and mucosa incorporation was present in all sutures (Figure 3D). Air leak was detected in three animals, which was corrected with additional stitching.

Discussion

The esophagus is a fragile organ given its specific morphological characteristics and anatomical location, and it has been considered by surgeons something of a revered zone.[4] This probably supports the slower dissemination of video-assisted surgery in thorax when comparing to laparoscopy.[22] Similarly, transesophageal-thoracic NOTES inspires less enthusiasm that abdominal NOTES.

The transesophageal NOTES endorses the possible absence of transthoracic incisions. Avoiding the intercostal nevralgia, it brings the expectation of a potentially greater patient benefit in thorax then in the abdomen.[12] Descriptions in porcine model of transesophageal mediastinoscopy and thoracoscopy,[9,13] lung and pleura biopsy,[13] lymphadenectomy,[12,13] pericardial fenestration,[12] vagotomy and esophagomyotomy,[14] Heller myotomy,[15] esophageal wall resection,[16] with or without EUS help, can be founded in literature. Besides the possible benefits, this item discussion always involves the procedure main risks: the esofagotomy blind creation, the unpredictable thoracic side exit without the EUS or fluoroscopic assistance, and finally the possible devastating consequences of a leaking from an incomplete esophageal closure.

We hypothesized that a hybrid thoracic approach could get the benefits of reducing the number of transthoracic ports and simultaneously minimize the limitations and risks of a pure transesophageal approach. This study explores the combination of the peroral route with a single transthoracic port for a complex intra-thoracic procedure – segmental esophagectomy with esophago-esophageal anastomosis. The reduction of the usually used

4-5 trocars to a single transthoracic instrument was obtained with the conjugation of three main factors: the use of a telescope with a working channel for 5 mm instruments, the prone position adopted in detriment of the regular left lateral decubitus, and the coordinated helpful work of the peroral gastroscope instruments.

The prone position is being promoted because it allows gravity to provide exposure with minimal handling, giving a good esophageal visualization, simplifying dissection and reducing the operating times, without sacrificing the patient safety.[1] In our *in-vivo* experiments we also confirmed these benefits with no need of any accessory port for lung retraction, and the single transthoracic instrument was totally focused on esophageal surgery.

The great improvement explored in this study is the help provided by the peroral/transesophageal port. It starts with the endoscope transilumination for rapid esophagus identification by the thoracoscope, this step may be particularly helpful for direct visualization of a possible lesion area, orienting a more precise resection.[24] During esophageal dissection and mobilization the traction provided by the endoscopic tip in the luminal space and some slight movements also helped the telescope-oriented work. Usually in minimally invasive esophagectomy, the esophageal specimen is removed via a separated neck incision, in our experiments we did it perorally, and depending on its size we predict it can be done in humans too. But the more impressive contribution was during the anastomosis creation. The first stitch that in a conventional thoracoscopic procedure is frequently the most difficult was in our experience more straightforward, because of the posterior esophageal wall grasping and proximal traction provided by the gastroscope instruments. Furthermore, the tissue layers exposure, the counter-traction and the ability of needle retrieval and presentation to the telescope whenever necessary (beside some inadequacy of the endoscopic forceps for needle secure grasping) were all good technical potentialities revealed during experimentation. All *in-vivo* anastomosis had at least 10 sutures, and each stitch was tied with 5 knots, with total control of the knotting by the gastroscope image, from the thoracic entrance until its tissue adjustment. We found episodically the mucosal retraction and missing during the stitch passage, but we could ameliorate this aspect with crescent skills in coordination of the tissue exposure and the thoracic telescope movements. Another advantage of a peroral access is the possibility of immediate check for luminal patency of the anastomosis and identification of suspected weakness areas needing additional stitches. Moreover even the endoscopic delivery of conditioning agents at this time can be provided to facilitate healing, as has been proposed before.[25]

We believe this approach could be safely translated to humans once safeguarded the endoscope sterility and the use of an oropharyngeal overtube. As potential indications for this approach we would imagine benign lesions like leiomyomas, resistant strictures, GISTs, esophageal ruptures, complicated strange-bodies, esophageal atresia, or even some selected not advanced malignant esophageal diseases. Moreover, this technique could contribute to eliminate by now most of the current limitations of pure transesophageal NOTES, becoming it useful for other thoracic extra-esophageal conditions, namely in all those procedures previously attempted by thoracic NOTES approach. The combination of the peroral approach with one transthoracic access seems advantageous because of the availability of two distinct images of the same procedure, resulting in a more accurate and safe assessment of the intervention, mainly the anastomosis, in a delicated space as the thoracic cavity is. We also believe that reduction of the number of transthoracic ports to one is the maximal that we can expect in minimally invasive thoracic surgery for now. In fact, it is conventionally required to leave in place an external drain after any thoracic intervention in humans, this highlight the last pertinence of our transthoracic access.

In conclusion, this study confirms the feasibility of peroral transesophageal NOTES with assistance of a single-trocar to carry out segmental esophagectomy with complete, single-layer and end-to-end intrathoracic esophageal anastomosis in porcine model. Moreover, this study reinforces the logic, safety and pertinence of transesophageal approach to the thoracic cavity.

Capsule summary

What is already known on this topic:

- The transesophageal approach has been proposed as a natural orifice direct access to the thorax and mediastinum.
- Serious limitations remain related with esophagotomy creation and safety closure.

What this study adds to our knowledge:

- Segmental esophagectomy with complete, single-layer and end-to-end intrathoracic esophageal anastomosis is feasible by peroral transesophageal NOTES assisted with a single transthoracic trocar.
- This might represent a step forward in thoracic NOTES.

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Figures Legends

Figure 1. Phantom model built to simulate the thoracic cavity: **A**) porcine esophagus sectioned in its middle segment and positioned inside the phantom; **B**) phantom with the coverage.

Figure 2. *Ex-vivo* steps of a complete, single-layer, and end-to-end esophago-esophageal anastomomosis: **A**) grasping, positioning and traction of the distal esophageal extremity provided by the gastroscope for the first stitch passage (gastroscope view); **B**) sequential sutures and needle position for proximal extremity puncture (telescope view); **C**) knot-tying with the knot-pusher entrance monitored by the gastroscope image (gastroscope view); **D**) cutting of a knot edges by the telescopic scissors (telescope view).

Figure 3. *In-vivo* segmental esophagectomy and esophago-esophageal anastomosis procedure: **A**) esophageal segmentectomy (telescope view) ; **B**) esophageal segment being removed by the gastroscope (gastroscope view); **C**) external final examination under endoscopic transilumination (telescope view); **D**) endoluminal examination of the anastomosis (gastroscope view).

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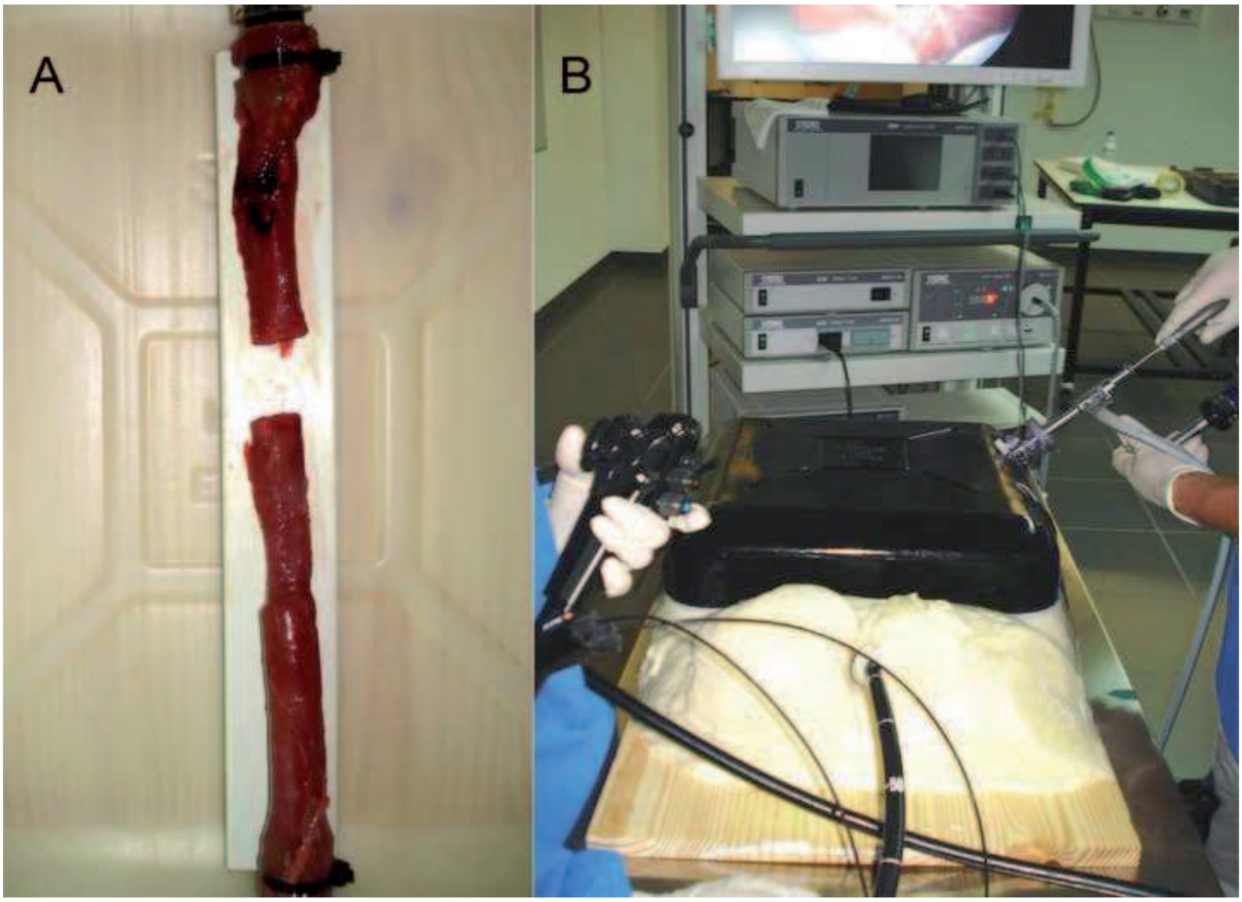

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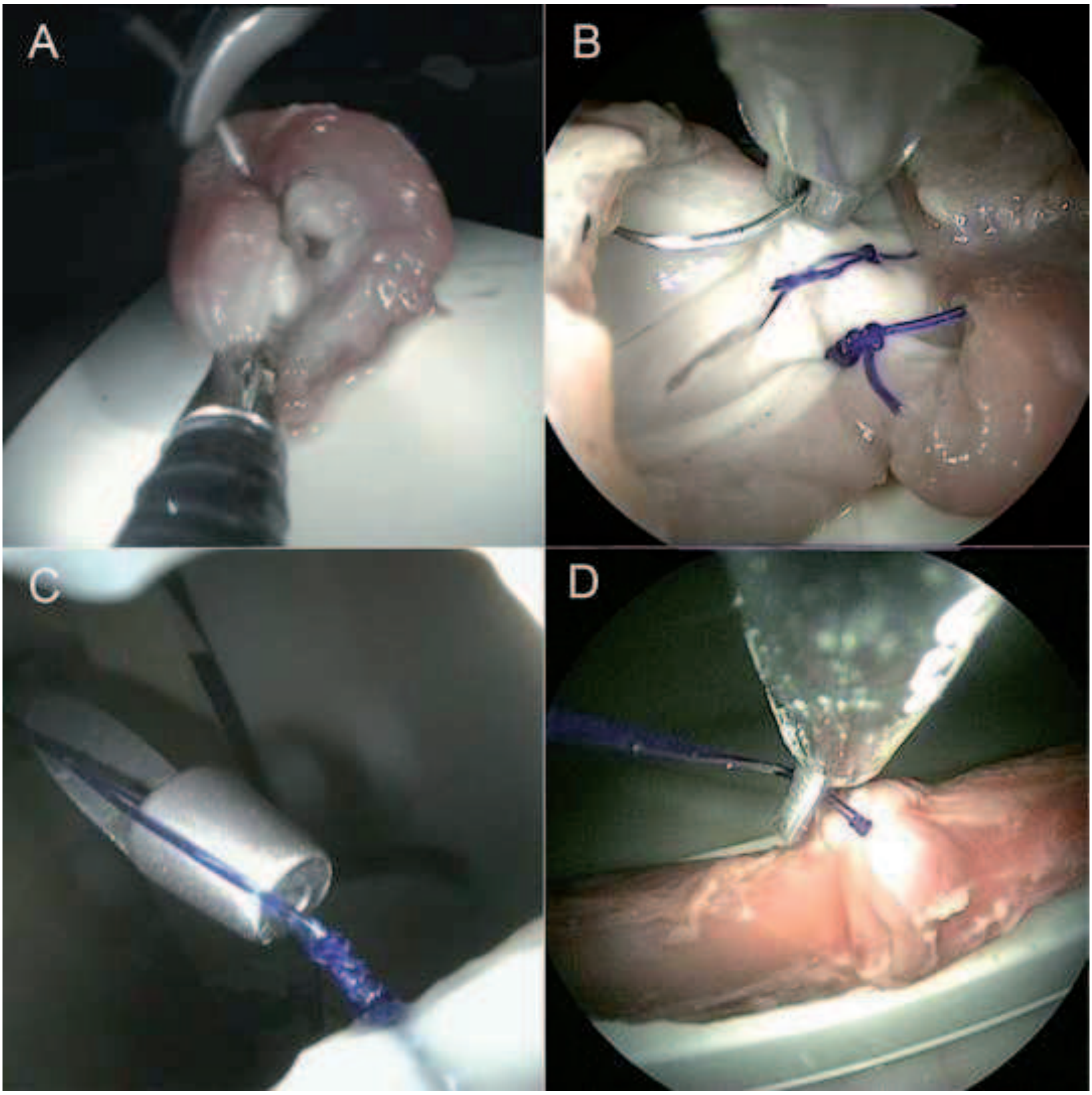

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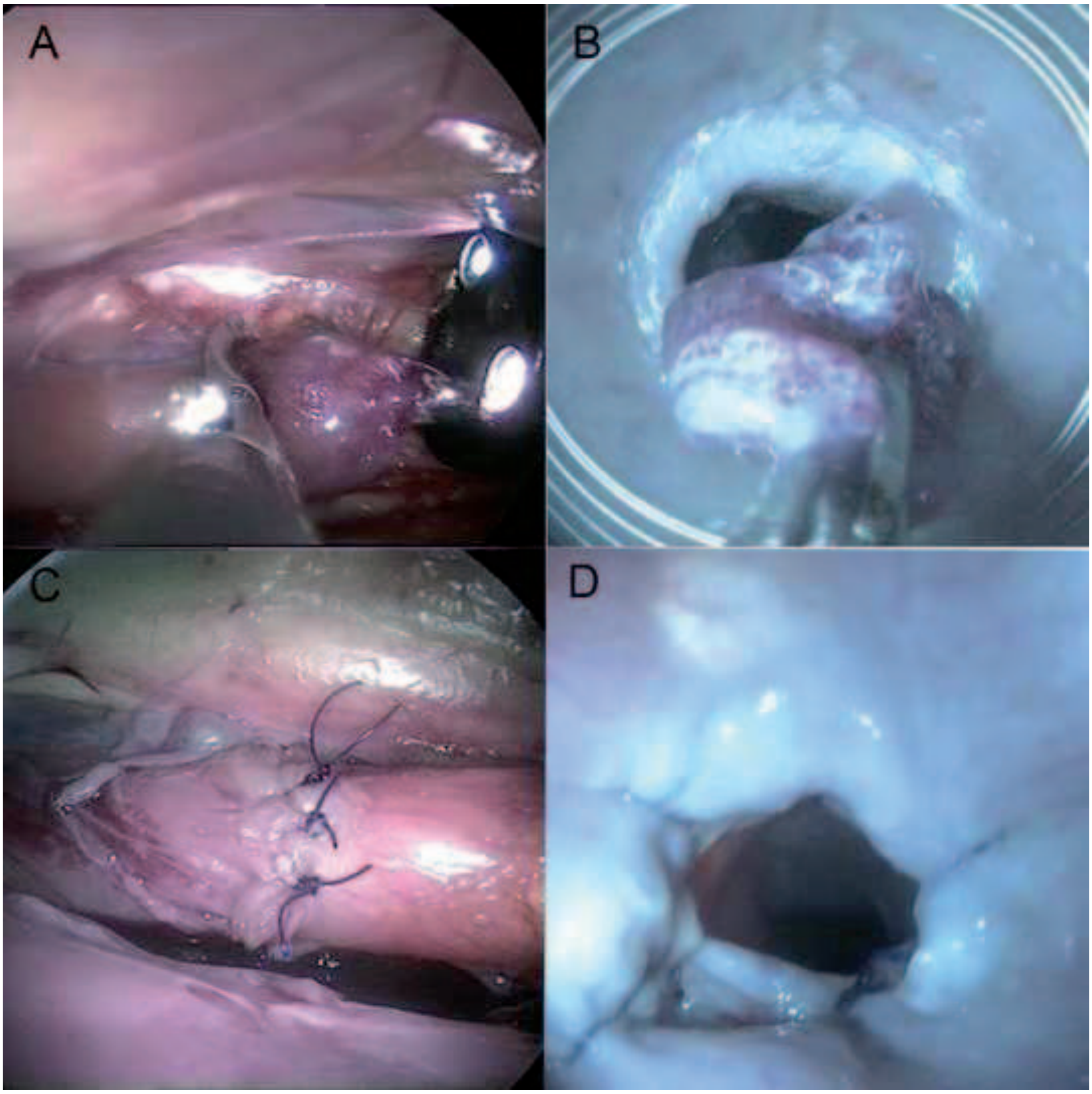

4. Appendices

Videos Legends

Video 1. The *in-vivo* telescope approach of the esophagus in prime screen and sequences of simultaneous gastroscope images in a secondary window. Using a scissors through the telescope working channel, with the help of transilumination and slight movements of the gastroscope for esophageal traction, it was possible to carry out a safe blunt dissection of esophagus from its adjacent structures. Sequentially it was then performed the proximal section of the esophagus, allowing the peroral transesophageal approach for grasping and traction of the distal esophageal stump, and the distal section completing the segmental esophagectomy. The specimen was removed perorally through an overtube as could be seen in the last images provided by the gastroscope.

Video 2. This video demonstrates some steps of a complete, single-layer, and end-to-end esophago-esophageal anastomomosis *in-vivo*, with gastroscope and telescope images sequentially intercalated. It starts with a gastroscope view of the first stitch needle passage on the proximal esophageal stump, posterior wall. Then, in a telescope image, can be seen the external grasping of the needle and the distal stump puncture, under gastroscope traction. Once the needle crossed transmurally both extremities, the sew edges were exteriorized for extracorporeal knotting. The gastroscope image was effective in monitoring the work of the knot-pusher introduced through the trocar, and the first stitch was completed after the edges cutting under telescope control. The following stitches were progressively easier to apply, here is presented a sequence of another proximal needle passage, knot-pusher entrance and stitch cutting in the second, third and fourth stitches respectively, completing most of the posterior wall by inside knoting. As the anastomosis evolved, the benefit of the gastroscope image was gradually reduced, but the procedure was also less demanding for the telescope.

The last sequence presented both sides needle passage, external knotting and cutting in the final stitches.

Video 3. This video presents the immediate anastomosis checking by inside and outside appearance at the end of the procedure in *in-vivo* experiments. Internally, can be seen the anastomosis patency and the mucosa incorporation in all sutures. Externally, the telescope was able to inspect the anastomosis surface over endoluminal transilumination, with the help of small rotations provided by the gastroscope.

PART III
discussion & conclusions

Chapter 8.
General Discussion

In 2006 NOTES was on the edge of medical community's interest, in a miscellaneous of curiosity and criticism. The concept of "incisionless" or "scarless" surgery catches everybody's attention with the first papers and oral communications presented in the most credited journals and meetings of the gastroenterological and surgical fields. At that time, a total of 20 studies reporting NOTES procedures, all in animal models, were present in the literature, and only 5 groups were devoted to NOTES investigation worldwide: Apollo group (Anthony Kalloo), Baltimore-USA; Lee Swanström group, Portland-USA; UK-Sweden group (Per Ola Park, Paul Swain); Christopher Thompson group, Boston-USA; and Correia-Pinto group, Braga-Portugal. The enthusiasm brought together different specialties (gastroenterologists, surgeons, urologists, gynecologists, anesthesiologists) sharing knowledge and experiences, attract the interest of the technological industry and push forward the motivation into reality. Thus all the good ingredients and a lot of work to do were there when our aims were delineated.

The initial studies, as have been said, highlighted four main limitations in transgastric approach demanding solution before a safe and effective translation to humans could be done. The one that immediately get our attention was the difficulty in tissue manipulation evidenced at the first experiments with more complex procedures, such as cholecystectomy. The simple gallbladder identification could be obtained in only around half of cases in the preliminary peritoneal explorations (Wagh et al. 2005). At the first cholecystectomy attempts there were exposed problems in obtaining a stable platform, adequate anatomic exposure, organ retraction, secure grasping, triangulation of instruments, and also in controlling the pneumoperitoneum (Park et al. 2005; Swanström et al. 2005). But cholecystectomy is one of the most common abdominal procedures and the standard for comparison is the laparoscopy. This represents a challenge and a key point for the ambitious NOTES implementation. For triangulation it would be necessary another instrument independent of the gastroscope dissector, furthermore for secure grasping and traction that instrument should be rigid. These premises could be obtained using a transgastric multitask platform or a combined approach – hybrid or pure NOTES. The multitasking platforms were already in development, Swanström et al presented the first prototype of a flexible trilumen guide with ShapeLock technology, which allowed the use of two 5 mm flexible endosurgical instruments and an independent ultraslim endoscope (Swanström et al. 2005). But the sole 33.3% success rate for cholecystectomy proved the platform needing of amelioration. By its turn Park et al exposed their difficulties in combining two flexible endoscopes both, on transgastric ports, and also explored the hybrid using a transabdominal trocar in combination with the transgastric port (Park et al. 2005).

Believing in pure NOTES benefits, we decided to combine two abdominal accesses on diametrically opposed natural orifices, the transgastric port and a lower abdominal port for rigid instrumentation and triangulation. In lower approach there were three possible options: the transvaginal, the transvesical and the transcolonic. Despite these accesses share the possibility of introducing rigid instruments into the abdomen, by our experience the transvesical port have some advantages (Lima et al. 2006; Lima et al. 2009a). It appears at the most anterior position in the sagital plan and for this reason gives the possibility to work above bowel loops with less risk for viscera damage. Additionally, the transvesical port is the unique lower abdominal access that is naturally sterile, and available in both genders in contrast to the transvaginal access. However, the transvesical port does not allow specimen retrieval as transvaginal and transcolonic, but for minor procedures or to work as an accessory port seems very promissory.

We advanced through our first aim with the study of cholecystectomy by a combined approach - transgastric and transvesical. It was demonstrated that the forward-viewing rigid instruments introduced throughout the transvesical port easily identify the gallbladder, providing upward retraction of its fundus, and good visualization of the cystic duct and vessels. The possibility of coordinated gallbladder mobilization in various axes, exposing different areas for gastroscope dissection, minimized the problems experienced when using the isolated transgastric access; however we still needed to work on a retroflexed position. Another advantage was the possibility to work under a pressure-controlled CO_2 pneumoperitoneum provided by the transvesical equipment, overcoming the problem of uncontrolled gastroscope air insufflation. And finally, a last benefit related to ports creation, transvesical port was described using an atraumatic Seldinger technique; then under CO_2 pneumoperitoneum and with the open front view provided by the transvesical port, it was possible the displacement of the abdominal wall from the stomach and to perform the gastrotomy with good external image control, making this step more safe. (Aims 1 and 2 - Chapter 4).

We demonstrate the usefulness of combining two natural orifices for moderately complex surgical procedures, reinforcing the feasibility of exclusive natural orifices transluminal endoscopic cholecystectomy, yet with common equipment. Following this idea we decided to test the feasibility of an even more complex intervention - nephrectomy - using the same strategy. And we found vital the coordination of the two ports operators to open the peritoneum, dissect the hilum and even more delicate, the vessels ligation. We individualized each vessel and ligated them with an ultrasonic scissors. This rigid laparoscopic instrument gets access by the transvesical port, under gastroscope image guidance. The possibility to introduce rigid laparoscopic ligation instruments revealed to be advantageous and was originally explored in this work (Lima et al. 2007b). In fact, one current limitation of all NOTES equipment developments is the difficulty to introduce reliable ligation instruments as they cannot easily be flexible. (Aim 2 - Chapter 5).

Our research also corroborates other author's descriptions while working with other ports, confirming that the lower abdominal and short way ports are better for surgeries in the upper abdomen and are able to provide rigid instrumentation when necessary (Fong et al. 2007; Marescaux et al. 2007; Wilhelm et al. 2007). They offer an en face orientation to the upper abdominal organs allowing better visualization and the ability to work straightforwardly. Otherwise the transgastric port, a long way port, require necessarily flexible or semi-flexible equipment and are better for approaching the pelvic or inferior abdominal structures (Jagannath et al. 2005; Wagh et al. 2006; Sumiyama et al. 2006). This is particularly true for simple surgical procedures, the ones that in laparoscopy needs up to 3 trocars and in NOTES could be performed with a single natural access. By counterpart, we advance that moderately complex procedures, needing 4 or more trocars in laparoscopy are not able to be performed by the current concept of flexible scopes and needs combination - hybrid or pure natural orifices, at least before more effective multitasking platforms became available. Currently there are some companies like Karl-Storz, Olympus and USGI with platform prototypes for transgastric NOTES under investigation, but still very complex and cumbersome (Swanström et al. 2009). It can even be discussed the risk-benefit of such huge and complex equipment versus the combination of more simple and intuitive, although efficient, instruments through different accesses. (Aim 2 - Chapter 4).

Our early work was centered on tissue manipulation and technical aspects of surgery, but they were non-survival studies. The subsequent step, conjecturing the Humans' translation of the transgastric surgery, was the survival challenge and for that purpose the 3 other points gain supreme importance: prevention of infection, access creation and visceral closure.

In the field of infection, pig studies are probably the extreme of luminal contamination and peritoneal dissemination risk (Simopoulos et al. 2008). The human stomach is usually empty and clean after some hours of starvation, and some studies analyzing the bacterial load admit that the transgastric endoscopic peritoneoscopy does not require decontamination of the stomach in humans (Narula et al. 2008). We found difficult to obtain a clean stomach in the porcine model, and it was necessary a progressive improvement in measures for this achievement. The disinfection of equipment was optimized, but we didn't use overtubes or subsequential antibiotherapy, aspects that can be ameliorated in humans' translation. (Aim 1 – Chapter 6).

The safe creation of the gastrotomy is another key issue, several transgastric access procedures have been described using sphincterotome or balloon dilation (Kalloo et al. 2004), endoscopic ultrasound guidance (Fitscher-Ravens et al. 2006), submucosal tunnel (Sumiyama et al. 2007), and PEG-like approach (Kantsevoy et al. 2007). However there is a common step in all descriptions, the use of a needle-knife with cautery for perforation, and its blind use is risky for adjacent organs, vessels and anterior abdominal wall. In our studies we used two working methods: when performing combined approach we monitored the gastrotomy creation with the image provided by the transvesical port (Rolanda et al. 2007; Lima et al. 2007b); when the aim was performing isolated transgastric surgery we used blind needle-knife with balloon dilation technique, preceded by Veress needle pneumoperitoneum for at least displace the internal structures from the stomach wall (Rolanda et al. 2009). Fortunately, we had just some cases of anterior abdominal wall injury, but this uncertainty is not acceptable for human application. Endoscopic ultrasound (EUS) had been suggested to overcome this aspect (Fritscher-Ravens et al. 2006), but EUS is not a generalized technique, and we believe that for the moment a safe and practical method for gastrotomy in humans shall be under visual control, what could be achieved with transabdominal ports in case of transgastric hybrid (Asakuma et al. 2009) or transvisceral in combined approaches (Rolanda et al. 2007; Lima et al. 2007b). For simple procedures using only transgastric access, this could be done using the PEG-like technique, it can be more cumbersome and also blind, but certainly gets a better control of the procedure. To date, no studies have addressed the problem of optimal location points of access, but usually the anterior gastric wall of corpus or antrum is the chosen place. This is not always accomplished in porcine model because of anatomical differences and easy gastric torsion, and in our experiments we frequently found posterior locations at necropsy (Rolanda et al. 2009). We also believe that in humans the orientation should be easier and the PEG-like technique can help in this point too. (Aim 1 – Chapter 4, 5 and 6).

But after all, the most crucial and less established part is the insurance of an adequate closure of the gastric defect. In fact, the most limiting factor for human translation is the gastrotomy efficient closure. It likely justify the still scarce number of successful reports of transgastric NOTES in humans. Regarding closure techniques several methods have been proposed and are under scientific appraisal in experimental models or under early clinical evaluation. These include the use of conventional endoscopic clips (Kalloo et al. 2004), over-the-scope clips (Shurr et al. 2008), septal occluders (Perretta et al. 2007), T-Tags and T-Bars for tissue opposing (Bergström et al. 2008; Dray et al. 2008), as well as more complex suturing devices as Eagle Claw VII (Chiu et al. 2008), NDO plicator (McGee et al. 2008), USGI Endosurgical Operating System (Bardaro et al. 2006) and linear endoscopic stapler (Magno et al. 2007). Moreover, special techniques in gastrostomy creation and closure such as using a submucosal endoscopy with an offset exit (Sumiyama et al. 2007), a PEG technique combined with a gastropexy (Sporn et al. 2008), or omentoplasty (Dray et al. 2009) had been suggested as a way to enhance the closure method. However, most of these devices and techniques still have limitations that need amelioration once most of them are too complex to apply or were not able to prove their effectiveness in survival studies.

The OTSC system is an equipment developed for the treatment of non-intentional perforations and bleeding lesions in GI tract, and is approved for clinical use (Kirschniak et al. 2007). Given its characteristics, we considered it appellative and apparently reliable to employ in case of single transgastric port use for simple procedures, even with regular endoscopes. Aiming to test the efficacy and reliability of OTSC system in vivo for gastric closure purposes, we decided to apply the OTSC in a survival porcine model after performing a simple pelvic procedure. We had confirmed its simplicity and intuitive application, like a variceal banding system adjusted to a regular endoscope; this is a valuable factor before the development of specific scopes for NOTES. Although with the system on the tip, the endoscope comprises an external diameter of 18 mm, an important fact to consider in avoiding esophageal trauma. The design of our study explored the gastrotomy dimension versus the clip size and number, creating 3 groups with 5 pigs each and followed the animals in a fifteen days survival period, after which they were sacrificed and necropsy performed. We obtained a 100% success in the groups with the binomial: 13 mm gastrotomy – 1 clip (12 mm), and 18 mm gastrotomy – 2 clips (12 mm). The group where we attempted to close a 18 mm gastrotomy with just 1 clip (12 mm) reverted in 2/5 situations of incomplete closure. We concluded that the OTSC® system revealed easy and efficient in gastrotomy closure in a survival experimental model, when correctly matched the gastrotomy dimension with the clips size and/or number. (Aim 4 – Chapter 7) .

This survival study also enhanced a new transgastric simple procedure in the lower abdominal cavity, a model that we had created for experimental varicocelectomy. This reinforced the idea of the privileged position provided by the transgastric port for the pelvic cavity, but also confirmed the feasibility of simple surgical procedures with a single transgastric port. (Aim 2 and 3 – Chapter 6).

Our work presented the feasibility of novel surgical techniques using pure NOTES peritoneal approach, the cholecystectomy, nephrectomy and the varicocelectomy, even with unconventional surgical tools. (Aim 3 – Chapter 4 and 6).

The laboratory research unshackles the dream, builds the substrate, and supports the training when big transformations are pictured in the horizon; another possible trail is the indolent transformation directly in clinical practice. In fact, in NOTES territory both perspectives are in course. While our and some other groups devoted pure NOTES lab investigation progress, the slow motion of hybrid NOTES started and disseminates in Humans. The first Human NOTES appendectomy communicated by Rao and Reddy in 2003 led the way to other pioneering works in humans. In true words it was a hybrid approach, as were most of following human experiences, namely the first transvaginal cholecystectomy performed by the IRCAD group in Strasbourg (Marrescaux et al. 2007), and the majority of transvaginal and transgastric cholecystectomies successfully performed with varying amounts of transabdominal assistance, around the Europe, Latin America, India and United States. Although, in literature there are around 20 publications reporting human procedures undertaken: transvaginal cholecystectomies and appendectomies, transgastric cholecystectomies and appendectomies, and other procedures including peritoneoscopy (transvaginal, transgastric and transvesical), transvaginal nephrectomy and sigmoidectomy (reviewed by Sodergren et al. 2009; Asakuma et al. 2009; Horgan et al. 2009; Gumbs et al. 2009). In most of these reports the strategy is hybrid (with at least one abdominal instrument). The hybrid approach became a transitional process in reducing the number of transabdominal ports, getting natural orifice experience without loosing triangulation and safety, until more robust and adequate technologies develop. The numbers evidenced the predominance of the transvaginal in detriment of the transgastric attempts, the basis for that is the recognized safety of the old well known transvaginal approach for gynecological interventions. Even though not published the first pure transgastric surgeries in humans are already claimed by Swanström using a USGI multitasking platform for cholecystectomy and performing also endoscopic gastrotomy suturing, but this technique still needs to be tested by other groups before it could be considered safe.

Thus far, with probably some exceptions, all these procedures were performed under Institutional Review Board approved protocol and supervision, with minor morbidity and no mortality reported. Otherwise, the advantages of laparoscopy appeared to be enhanced by this approach, so these results are encouraging and cause enthusiasm for the future widespread application of NOTES (Swanström et al. 2009).

In contrast to abdominal NOTES, the course of thoracic NOTES is being more slower and prudent. In fact, even thoracoscopy had not conquest a global acceptance for certain surgeries in virtue of its substantial learning curve (Song et al. 2009), thus until now the peroral approach has not yet been focus of humans translation attempts. In animal model there are descriptions of transvesical-transdiaphragmatic thoracoscopy and lung biopsy (Lima et al. 2007a) and transgastric-transdiaphragmatic pericardial fenestration, but the more reasonable reported access is the transesophageal approach. The NOTES transesophageal access endorses the possible absence of transthoracic incisions avoiding the intercostals nevralgia and brings the expectation for a potentially greater patient benefit in thorax then in the abdomen. It may allow better access to central structures such as the pulmonary hilum and posterior mediastinum with a direct visualization of interested areas, instead of percutaneous pleural biopsy or video-assisted thoracoscopy that are respectively blind and more useful for peripheral lesions (Gee et al. 2008). However, considerably fewer studies had been devoted to NOTES evaluation and treatment of thoracic diseases even in porcine model, although descriptions of transesophageal mediastinoscopy and thoracoscopy (Sumiyama et al. 2007; Gee et al. 2008), lung and pleura biopsy (Gee et al. 2008), lymphadenectomy (Fritscher-Ravens et al. 2007; Gee et al. 2008), pericardial fenestration (Fritscher-Ravens et al. 2007), vagotomy and esophagomyotomy (Woodward et al. 2008), Heller myotomy (Pauli et al. 2008), and full-thickness esophageal wall resection (Fritscher-Ravens et al. 2009) can be founded in literature. The access was achieved using the submucosal tunnel initially described by Sumiyama or using EUS control, and the esophagotomy closure was precariously accomplished with hemoclips on mucosal flap (Sumiyama et al. 2007; Gee et al. 2008; Woodward et al. 2008) or with t-tags (Fritscher-Ravens et al. 2009). Besides the possible benefits, the experiments also exposed the procedure main risks: the esofagotomy blind creation with danger for adjacent organs, the unpredictable thoracic side exit and finally the possible devastating consequences of an incomplete esophageal enterotomy closure (Perretta et al. 2009).

Thus, we hypothesized that a hybrid thoracic approach could get the benefits of the transthoracic ports number reduction and simultaneously minimize the limitations and risks of a pure transesofageal approach. So our last study explored the combination of the peroral route with a single transthoracic port for a complex intrathoracic procedure – a segmental esophagectomy with complete, single-layer, end-to-end esophago-esophageal anastomosis. This study become clear that it is possible a reduction from 4 transthoracic trocars to 1 single transparietal thoracoscope with working channel, mainly because of the great improvement provided by the peroral/transesophageal port. With its transilumination it helped the rapid esophagus identification by the thoracoscope and the orientation of a possible lesion area, also helped during esophageal dissection and specimen removal. But the more impressive contribution was during the anastomosis creation: the first stitch that in a conventional thoracoscopic procedure is frequently a challenge was, in our experience, more straightforward because of the posterior esophageal wall grasping and proximal traction provided by the gastroscope instruments. Furthermore, the tissue layers exposure, the counter-traction and the ability of needle retrieval and presentation to the thoracoscope when necessary were all good technical potentialities revealed during experimentation. Another advantage was the possibility of immediate check for luminal patency of the anastomosis, and identification of suspected weakness areas needing additional stitches. (Aim 4 and 5 – Chapter 7)

Finally, it has been confirmed the safe feasibility of a segmental esophagectomy with end-to-end intrathoracic esophageal anastomosis, preserving all basic surgical principles. We believe that this work demonstrated the pertinence and a step forward in the direction of thoracic NOTES, which can be very useful for benign lesions surgery like leiomyomas, strictures, GISTs, esophageal ruptures, complicated strange bodies, esophageal atresia repair, or even for other thoracic extra-esophageal conditions.

Chapter 9.
Future Directions

And now what do we envision for NOTES? To predict the future, it is also important to look back at the past, and the lessons garnered from laparoscopy have forecasted the need for caution. Well-managed human studies, preceded by a solid experience in animal models, need to be conducted to assure the safety and efficacy of pure NOTES in a clinical setting. It is important that this research be conducted in a way that minimizes bad publicity and describes both favorable and adverse outcomes. This is the line to avoid pitfalls and disqualification of an emerging and promising technique. In order for NOTES to gather sufficient momentum, the simpler procedures that would be safe to start with – such as diagnostic peritoneoscopy, liver biopsy, are unlikely to have sufficient volume to drive substantial change. In these three years, the laparoscopy evolved to single-port with articulated and semi-flexible equipment (reviewed by Raman et al. 2009), and the endoluminal endoscopic surgery gain an array of new tools (reviewed by Benhidjeb et al. 2008) and also the self-confidence of being able to solve most of intra-procedural complications, such as GI tract bleeding and perforation. Maybe interventional gastroenterologists (as is the case of this thesis' author) will be interested in translation for Humans of the majority of the abdomino-pelvic procedures presented in this work, but before that occur, more work mainly from biomedical engineering is warranted. In the meanwhile, certainly the GI wall is no longer a barrier and the new instruments under development will be adopted for wall lesions dissection, resection, and suturing. How far NOTES will reach we don't know, but undoubtedly it is being a refresh in the surgical sciences, and the gastroenterologists in my opinion might be in the field.

Chapter 10.
Main Conclusions

At the moment, the real value of breaking through the boundary of the gastrointestinal tract wall to perform transgastric surgery still is uncertain. It is unclear whether this type of surgery, mainly more complex procedures, needs complex platforms with large instruments having more degrees of freedom and triangulation mechanisms, or whether a simple toolbox of new instruments can be created delivering effective surgery with combined natural orifices, as transgastric and transvesical. Reaching the gallbladder or other upper abdominal structures with an isolated transgastric approach seems difficult using conventional flexible endoscopes, but simple lower abdomen and pelvic procedures were proved to be feasible. An adequate suturing method is still needed for transgastric widespread application, but here was attested the interest of the OTSC system in selected gastrotomies. Finally has been confirmed the safe feasibility of a segmental esophagectomy with esophageal anastomosis, using the peroral esophageal approach combined with a single transthoracic instrument. This strategy might likely work as an intermediate step for thoracic NOTES Humans' translation.

PART IV
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