REVIEW

Natural orifice transluminal endoscopic surgery (NOTES): current experience and urologic applications

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CASELLA DP, SMALDONE MC, AVERCH TD. Natural orifice transluminal endoscopic surgery (NOTES): current experience and urologic applications. The Canadian Journal of Urology. 2010;17(3):5151-5161.

Natural orifice transluminal endoscopic surgery (NOTES) has attracted considerable recent attention for its potential to allow traditional abdominal procedures to be performed without a transabdominal incision. With considerable experience in the development and application of minimally invasive techniques, urologists have played a significant role in early experimental NOTES efforts and have contributed to early investigations in human subjects accordingly. However, adoption of these techniques has been limited due to cumbersome endoscopic equipment and concerns regarding peritonitis from failed viscerotomy closure. Experience with use of NOTES in human subjects is limited, and studies comparing NOTES to conventional minimally invasive techniques are lacking. Until adequate endoscopes are developed to facilitate a pure NOTES approach, multiple portals of entry will be necessary to facilitate both urologic and non-urologic reconstructive and extirpative procedures. Our aim is to evaluate NOTES techniques, portals of entry, early clinical experiences, and the application of NOTES to urologic surgery.

Key Words: NOTES, minimally invasive surgery, outcomes, urology

Introduction

Minimally invasive surgery has dramatically evolved over the past two decades, and randomized clinical trials comparing open and laparoscopic procedures have demonstrated reduction in post operative pain, faster convalescence, and a decreased frequency of wound related infections.[1] With increasing experience and improvements in technique, complex reconstructive procedures performed via a laparoscopic or robotic assisted route have become routine across surgical subspecialties. Natural orifice translumenal endoscopic surgery (NOTES) has attracted recent interest for its potential to allow intra-abdominal surgical procedures to be performed entirely through a natural orifice, facilitating "scarless" or truly minimally invasive surgery. Interest in endoscopic intra-peritoneal procedures developed from the observation that minimal sequelae resulted from accidental viscerotomies during gastroscopic and colonoscopic resections.[2] This idea has conceptually evolved to comprise insertion of an endoscopic instrument through a natural orifice (mouth, anus, vagina, urethra), followed by viscerotomy to gain intraperitoneal access.[3] Although the premise is simple, the reality of performing these procedures is severely limited by access to the target organ, developing technologies, and the potential for catastrophic infectious complications. For these reasons current investigations are in early development, and application in human subjects

Accepted for publication January 2010

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has only recently been reported.[4-6] The goal of this article is to evaluate current experimental NOTES techniques, the potential advantages and limitations of the differing portals of entry, review early clinical experiences, and discuss the application of NOTES to urologic surgery.

Considerations with natural orifice surgery

Proposed advantages of NOTES over traditional open and minimally invasive techniques are primarily the result of avoiding transabdominal incisions. Benefits include reduced incidence of surgical site infections, intra-abdominal adhesions, incisional hernias, and post surgical scarring for improved cosmesis.[2] Quality of life benefits include reduced postoperative pain, need for anesthesia and analgesia, and earlier convalescence.[3] Economic considerations include a reduced cost of hospital stay and postoperative complications, and the ability to perform more same day or outpatient procedures. With increasing experience, NOTES procedures may also be more efficacious in morbidly obese patients in which a abdominal incision is not feasible or critically ill patients that are too unstable to be transported from the intensive care unit.[2,3] It is important to clarify that these potential benefits are speculative in nature since evidence from randomized prospective clinical trials are lacking to support any benefit over traditional surgical techniques.

Initial experimental studies using porcine models have demonstrated technical feasibility of a wide range of NOTES procedures. However, these reported successes primarily consist of trial and error techniques performed with flexible endoscopic instruments. Several factors need to be considered when choosing a portal of entry, including ease of access, potential for infectious complications, security of closure, maximum diameter for instrument insertion and specimen retrieval, and relation to target anatomy, Table 1.[3] Compared to contemporary laparoscopic and robotic assisted platforms, NOTES is limited by reduced visibility, maneuverability, and ability to triangulate instruments. Lack of adequately designed instrumentation is a major impediment to clinically adopting these techniques

TABLE 1. **NOTES portals of entry with respective advantages and disadvantages**

Transvaginal advantages	**Transgastric**	**Transcolonic**	**Transvesical**
Direct visualization of upper abdomen	Direct visualization of pelvis	Direct visualization of upper abdomen	Direct visualization of upper abdomen
Familiar anatomy	Familiarity with conventional equipment	Suitable for specimen extraction	Familiar anatomy
Minimal risk of peritonitis			Minimal risk of peritonitis
Reliable access and closure techniques			Familiarity with conventional equipment
Few limitations to rigid and flexible instrumentation			
Suitable for specimen extraction			
Disadvantages			
Only applicable in less than 50% of patients	No reliable technique for gastrotomy closure	No reliable technique for colostomy closure	No reliable technique for cystotomy closure
Unknown effects on patient fertility and sexual function	Risk of peritoneal contamination	Risk of peritoneal contamination	Unsuitable for large specimen extraction
Need to reposition patient	Unsuitable for large specimen extraction		
	Retroflexion needed to visualize upper abdomen		

and is the focus of considerable attention in current investigations. In addition to being more technically demanding, described techniques of NOTES entry and access closure have significant associated risks of peritoneal contamination and infectious complications regardless of portal of entry. In addition, NOTES is also subject to the known risks of traditional laparoscopic access including air embolism, vascular, and visceral injury.[7] Techniques to control portal of entry sepsis lack a standardized approach in current studies. Although these techniques need to be tailored to specific entry sites, they will likely include antibacterial lavage in addition to intravenous antibiotic prophylaxis.[8] It is clear that further developments in endoscopic instrumentation and investigations examining access and closure techniques are vital to the continued evolution of NOTES and its integration into clinical practice.

Transvaginal access

Considerations

Culdoscopy, or transvaginal access to the abdominal cavity, been utilized in various forms since the early 1900's,[9] and has evolved to encompass outpatient diagnostic procedures for evaluation of infertility with modest incidences of access failure or complications documented in large series.[10] Advantages to a transvaginal approach include ease of access, reliable secure closure methods with minimal risk of infectious complications, direct line of sight relationship to target anatomy, and maximal diameter for instrument placement and specimen removal.[11] The vagina has already been utilized for specimen removal in traditional extirpative laparoscopic procedures, including cholecystectomy.[12] Gill et al reported a series of 10 patients undergoing laparoscopic nephrectomy with vaginal specimen extraction. Removal of the surgical specimen and colpotomy cloure required repositioning in the supine position but was able to be performed efficaciously (mean 35 minutes), with no postoperative complications and minimal patient discomfort.[13] Vaginal extraction has subsequently been described for a number of urologic procedures including nephroureterectomy[14] and cystectomy.[15]

In appropriate subjects vaginal access may be optimal when compared to other NOTES portals of entry. Significant concerns exist regarding the infectious risks of gastrointestinal contamination of the peritoneum with NOTES access; furthermore, lack of reliable gastrotomy and colostomy closure mechanisms has limited the clinical application of NOTES in human subjects. In contrast, reliable reproducible techniques of gaining transvaginal intraperitoneal access have been described with minimal complications[16] and a secure, watertight closure of the vaginal cuff with minimal infectious sequelae is attainable utilizing traditional instrumentation.[17] It has also been postulated that closure of the vaginal cuff may be unnecessary following gynecologic procedures and that spontaneous colpotomy closure is possible without negative sequelae.[18] Despite enthusiasm regarding this approach, there are special considerations with transvaginal NOTES procedures which currently remain unaddressed, including upper abdominal bacterial contamination as well as quality of life and sexual function following a vaginal incision. Another significant disadvantage is that transvaginal access can only be utilized in less than 50% of patients. In addition, there are well documented contraindications to obtaining transvaginal access, including obliteration of the pouch of Douglas, a fixed retroverted uterus, and previous cervical or pelvic radiation.[10,11] Despite these limitations, of all NOTES portals of entry, a transvaginal approach is currently the most applicable to human study.

Early porcine and human experiences

Early porcine experiments have demonstrated the feasibility of a transvaginal approach to perform NOTES urologic procedures, Table 2. In the first published work, Gettman et al reported their experience performing six transvaginal nephrectomies in four female pigs. In one case a nephrectomy was completed utilizing a single transvaginal port whereas in the other five cases an additional 5 mm transumbilical port was utilized for visualization and instrument triangulation. In all cases the specimen was extracted from the vagina and in no instance was the vagina closed.[19] Subsequent porcine experiments have been described including a nephrectomy via an umbilical port and transvaginal TransPort Multi-Lumen Operating Platform (USGI Medical, San Clemente, Ca),[20] pure NOTES transvaginal nephrectomy[21] and cholecystectomy[22] using magnetically anchored instruments, and pure NOTES retroperitoneal nephrectomy[23] and adrenalectomy.[24] In each investigation above, the authors concluded that upper abdominal and retroperitoneal renal surgery is technically feasible via a transvaginal approach with minimal sequelae, with the caveat that available instrumentation currently limits step application to human studies.

Attempts to overcome equipment limitations have led to the investigation of combined NOTES procedures utilizing hybrid dual access in porcine models. Successful performance of combined transgastric and tranvaginal procedures including nephrectomy[25,26] and renal cryosurgery[27] have recently been described.

TABLE 2. **Urologic porcine NOTES investigations**

Study	Portal of entry	No. subjects/ No. experiments	Hybrid vs. dual NOTES vs. pure NOTES	Urologic procedure	Complications
Gettman et al[19]	TV	4/6	5/6 hybrid – 5 mm midline port 1/6 Pure NOTES	Nephrectomy	Vascular injury (1)
Lima et al[61]	TG, TVE	6/6	Dual NOTES	Nephrectomy	None
Clayman et al[20]	TV	1/1	Hybrid 12 mm midline port Multi-lumen operating platform	Nephrectomy	None
Isariyawengse et al[25]	TG, TV	1/2	Dual NOTES	Nephrectomy	None
Crouzet et al[27]	TG, TV	2/4	Dual NOTES	Renal cryoablation	None
Haber et al[29]	TV	10/30	Hybrid 2.6 cm umbilical port da Vinci platform	Pyeloplasty (10) Partial nephrectomy (10) Nephrectomy (10)	None
Box et al[28]	TV, TC	1/1	Hybrid 12 mm midline port da Vinci platform	Nephrectomy	None
Raman et al[21]	TV	2/2	Pure NOTES MAGS stabilized Platform	Nephrectomy	None
Perreta et al[23]	TV	10/10	Pure NOTES	Nephrectomy	None
Perreta et al[24]	TV	2/4	Pure NOTES	Adrenalectomy	None
Haber et al[26]	TV	5/5	Pure NOTES	Nephrectomy	None

TV = transvaginal; TG = transgastric; TVE = transvesical; TC = transcolonic

Other recent novel investigations have included the application of the da Vinci platform (Intuitive Surgical, Sunnyvale, CA) to NOTES procedures. Box et al recently reported a porcine nephrectomy utilizing the da Vinci S robot through a single 12 mm umbilical port and two 12 mm transvaginal and transcolonic ports, with the intact specimen removed via the vagina. Since this was an acute non-survival experiment, closure of the colpotomy was not addressed.[28] In a similar application, Haber et al recently reported their experience performing reconstructive urologic procedures (10 pyeloplasties, 10 partial nephrectomies, and 10 nephrectomies) using a single 2 cm umbilical incision and a second robot arm placed through a vaginal port in a porcine model.[29] While they were able to avoid use of a transgastric or transcolonic port, the mean size of the umbilical incision was 2.6 cm. However these applications demonstrate that hybrid transvaginal procedures may be most ready for widespread human application.

Over the past 5 years, the first small clinical series of successful transvaginal human cases have been reported. There have been multiple reports of hybrid transumbilical and transvaginal cholecystectomies,[30,31] and recently the performance of a pure NOTES cholecystectomy was described.[32] Urologic procedures in human subjects, primarily nephrectomies through a hybrid approach, have also been recently reported, Table 3. In 2008 Branco et al described their experience performing a NOTES simple nephrectomy via a transvaginal port with two additional 5 mm abdominal ports in a 23-year-old female with a nonfunctioning chronically infected right kidney.[33] In this case report the total procedure time was 170 minutes with an estimated blood loss of 350 cc without intraoperative or postoperative complications, and the patient was discharged 12 hours following her procedure. In 2009, Kaouk and colleagues reported performing a hybrid NOTES transvaginal nephrectomy utilizing an additional 5 mm umbilical port needed for colon

TABLE 3. **Urologic human NOTES investigations**

Study	Portal of entry	No. subjects	Port placement	Urologic procedure	Complications
Gettman et al[75]	TVE	1	Hybrid standard RALRRP port placement	Peritoneoscopy	None
Branco et al[33]	TV	1	Hybrid 5 mm abdominal ports x 2	Nephrectomy	None
Kaouk et al[34]	TV	1	Hybrid 5 mm abdominal port x 1	Nephrectomy	None
Sotelo et al[35]	TV	4	Hybrid 5 mm umbilical port upper pole	Nephrectomy	Renal injury (1) failure to progress (1), hemorrhage (1)

TV = transvaginal; TVE = transvesical; RALRRP = robotic assisted laparoscopic radical retropubic prostatectomy.

retraction and lysis of adhesions.[34] Total operative time was 307 minutes, there were no complications, and the patient was discharged home after 23 hours. In the largest series to date, Sotelo et al reported the performance of transvaginal NOTES procedures utilizing a transumbilical assistant port in four women.[35] Unfortunately, the first three procedures were converted to standard laparoscopy due to rectal injury during vaginal entry, failure to progress, and upper pole bleeding. These complications illustrate that there is a very steep learning curve with the application of novel surgical techniques and that judicious caution is necessary with the application of NOTES in human subjects. In all of the above experiences transvaginal access was obtained through a posterior colpotomy using traditional instruments with primary closure of the vaginal wall. While encouraging results have been reported, it is doubtful that pure transvaginal NOTES urologic procedures will be possible until improved instrumentation is available.

Transgastric access

Considerations

Enthusiasm for transgastric access to the peritoneal cavity was predicated on long term success with performing percutaneous endoscopic gastrosomy tube placement and the low associated risk to surrounding visceral structures when performing an anterior wall gastrotomy.[36] Due to familiarity with gastroscopic techniques, the transgastric route was a natural choice for early NOTES porcine investigations.[8] However, early barriers to success in these studies included endoscopic access to the peritoneal cavity, visualization of the upper abdomen, and endoscopic gastrotomy closure.[37]

Described gastrotomy techniques for transgastric peritoneal access include blind puncture with an electrosurgical needle knife followed by dilation of the resultant transmural access tract with either a sphincterotome or wire guided dilating balloon.[38,39] Although creation of a transmural gastrotomy facilitating endoscope placement is feasible and reproducible, there are several implicit risks to these techniques including risk of hemorrhage, leakage of insufflation through the access point, and difficulty reapproximating the gastrotomy edges.[40] An additional observation in early porcine experiments was that visualization of the upper abdomen, including the retroperitoneum, is limited with transgastric peritoneal access. In contrast to pelvic organs which are in the direct line of vision of a transgastric endoscope, retroflexion is required to access the upper abdominal structures, limiting available instrumentation and resulting in a more technically challenging procedure.[41] Instrument design limitations including excessive flexibility as well as inadequate grasping and retraction technology also restrict the performance of complex reconstructive procedures at this time.[42]

Multiple techniques of creating a watertight gastrotomy closure have been described in early NOTES investigations. In the earliest reported porcine feasibility studies, spontaneous closure[38] and use of simple endoscopic clips to approximate the gastrotomy edges[39] were described, although there are concerns that existing endoscopic clips may not reliably be able

to grasp the thickened and edematous stomach edges following a long procedure and prevent peritoneal contamination. Although iatrogenic and pathologic gastric perforation have been reported to spontaneously heal with conservative measures, limitations in current endoscopic equipment coupled with the risks of peritonitis and sepsis prevent spontaneous closure from being a viable option in human trials. Various novel endoscopic suturing devices have been developed to achieve a full thickness stomach closure, including T-tag tissue anchor systems,[43,44] the EndoCinch device (Davol, CR Bard, Billerica, MA),[45] and the Eagle Claw device (Olympus America, Inc., Center Valley, PA).[46] While it is intuitive that a full thickness closure would provide a more water tight and durable repair, there is currently no accepted technique as each method is technically demanding and all remain experimental. Full thickness endoluminal stapler devices are currently under investigation but at this time length of stapler and device articulation are limited by the size of commercially available endoscopes.[47] Gastrotomy occlusion with a PEG tube[48] and omentoplasty[49] have also been described as potential less technically demanding closure techniques. It is possible that with technological advances, small caliber endoscopes may obviate the need for gastrotomy closure in the future.[40] Limitations with all of the described techniques include the potential for injury and perforation of organs outside the stomach due to blind needle puncture, limited ability to retroflex the endoscope with closure needles in the working channel, and chronic inflammatory effects of foreign bodies in the stomach wall.[50]

Early porcine and human experiences

In the first animal study reported, Kalloo et al described their initial experience performing transgastric peritoneoscopy and biopsy in a porcine model using endoclips to close the gastrotomy.[39] Subsequent porcine feasibility studies have included gastrojejunostomy,[51] lymphadenectomy,[52] partial hysterectomy,[53] oopherectomy and tubal ligation,[54] cholecystectomy,[55] appendectomy,[56] and splenectomy.[57] The majority of these studies were performed entirely through a transgastric access or as a combined approach in conjunction with a traditional transabdominal access port with no standardized method of gastrotomy closure. Although all of the above procedures were successfully completed using NOTES technology, a significant proportion were completed using trial and error techniques, and were often tedious and technically demanding to perform. In addition, although the endoscopic view afforded by a transgastric NOTES approach may facilitate pelvic urologic surgery, retroperitoneal extirpative and reconstructive procedures would be severely limited by the degree of retroflexion required to achieve adequate visualization. Therefore the general consensus is that this technology remains in its infancy, and until further technical advances are made, use in human subjects will be limited.

Investigations in human subjects have only recently been reported. In 10 patients scheduled to undergo diagnostic laparoscopy for evaluation of a pancreatic mass, Hazey et al reported successful transgastric access and diagnostic peritoneoscopy. They reported no complications related to access, and retroflexion prevented visualization of the upper abdomen in only two patients. Since all 10 patients proceeded to immediate exploration for palliation or definitive treatment of disease, these authors did not address the issue of gastrotomy closure.[58] In their case report Marks et al described successful replacement of a dislodged feeding tube at the bedside via a transgastric approach without complications at 30 days post procedure.[59] Intensive care unit patients represent an intriguing population for the application of these new techniques as they may obviate need for general anesthesia or avoid the morbidity of a more invasive surgical procedure. More recently, Sodergren et al reported their experience performing hybrid transvaginal and transgastric cholecystectomies in 16 patients (10 transvaginal, and 6 transgastric). With a mean operative time of 120 minutes, patients were discharged on the second postoperative day with no complications.[60] To date, urologic experience with transgastric NOTES has been extremely limited and has only been investigated in experimental models. In the earliest published report, Lima et al discussed the feasibility of performing four right and two left nephrectomies via a combined transgastric and transvesical approach in a non-survival porcine model.[61] They reported no complications with obtaining access, and were able to perform the hilar and ureteral dissection using ultrasonic scissors introduced through the transversical port in all cases. Although an interesting approach, the inability to remove the surgical specimen through either portal of entry limits its clinical utility at this time. Until further experience is demonstrated with gastrotomy closure techniques and improved instrumentation is developed, use of the transgastric approach in urologic surgery will remain investigatory in nature only.

Transcolonic access

Considerations

Theoretical advantages of transcolonic access include direct visualization of the upper abdomen, eliminating

the need for retroflexion and allowing for improved instrument stabilization compared to the transgastric technique. In addition, due to increased compliance and capacity, use of the colon for access facilitates placement of larger instruments as well as the removal of larger specimens.[62] Despite these potential advantages, the use of colon as a portal of entry raises significant concerns for peritonitis due to the increased risk of translocation of intraluminal bacteria or fecal contamination of the sterile peritoneal cavity.[63]

Early porcine experiences

Current consensus suggests that transcolonic NOTES is technically feasible. Fong et al were the first to describe their experience with transcolonic cholecystectomy in a porcine survival model. They reported successful gallbladder resection in all five cases, but following colotomy closure with endoscopic clips one animal required euthanization at 48 hours for suspected peritonitis.[41] In a separate porcine survival study Fong et al evaluated the use of colonic access for peritoneoscopy. Closing the colotomy site using endoscopic clips, endoloops, or a prototype closure device the authors reported no complications at 14 days post procedure. At autopsy, although the colonic incision sites were reported to be well-healed in all cases, incision related adhesions were identified in four of six pigs. Further, microscopic abscess and other inflammatory changes were seen at the closure site in all animals.[64] Additional studies performing distal pancreatectomy using a combined transcolonic/vaginal hybrid approach have also been reported.[65] The authors concluded that a transcolonic route provides improved endoscope stability and upper abdominal exposure compared to the transgastric route. However, these early experiences illustrate that transcolonic access requires improved full thickness closure techniques to reduce the risk of peritoneal fecal soiling and that further technological advances are needed prior to use in human subjects.

Wilhelm et al recently described an innovate technique to achieve sterile sigmoid access in a porcine model and facilitate leak-proof closure of the entry site. Following instillation of one liter of taurolidin solution (Taurolin, Boehringer Ingelheim, Ingelheim, Germany) and 2.5 liters of Ringers solution through a Veres needle, a modified transanal endoscopic microsurgery guide tube is introduced under ultrasound guidance to facilitate placement of a flexible endoscope. To ensure a secure closure, a purse string suture is placed around the colotomy site prior to removal of the tube and the closure is reinforced with a linear stapler. In the five survival subjects, there were no postoperative fevers or deaths, and at the time of euthanasia (10 days post procedure) the colonic incision sites were completely closed with no identified signs of inflammation, abscess, or peritonitis.[66] Compared to the transgastric route, the transcolonic approach shows promise for urologic application due to direct visualization and access to the retroperitoneum; importantly, unlike the transvaginal route, the transcolonic route can be utilized in all patients. Unlike the transvesical route, which is limited in luminal diameter for specimen removal, increased colonic compliance permits larger instrument placement as well as specimen retrieval.[62] With the current interest in developing less invasive surgical techniques, the NOTES transcolonic approach to the peritoneal cavity will likely play a major role across all surgical specialties. Feasibility and efficacy studies will be limited to animal models until a more reliable reproducible colotomy closure method can be demonstrated.

Tranvesical access

Considerations

There has been a recent surge of interest in the use of a transvesical portal of entry for NOTES procedures, primarily due to concerns regarding contamination of the peritoneal cavity with failed transgastric or transcolonic portal closure. There are distinct advantages of using the urinary tract compared to other portals of entry. The transvesical approach precludes the need for gastrointestinal closure which is currently experimental at best.[40] In addition, urine is sterile in a majority of patients, decreasing the risk of bacterial contamination of the peritoneal cavity. Similar to a transcolonic approach, transvesical access facilitates direct targeted vision of both the upper abdomen and retroperitoneum without the need for retroflexion.[67] Perhaps most relevant to the field of urology, urologists have long been facile with the use of a transurethral approach to bladder and prostate surgery, and familiarity with transurethral rigid and flexible instrumentation as well as robotic platforms currently in development[68] have contributed to recent interest in experimental models of transvesical NOTES.

It is important to address limitations to use of the bladder as a portal of entry. Although the risks of bacterial contamination should be less than gastrointestinal routes, risks of peritonitis and fistula formation are not insignificant and antibiotic sterilization regimens currently are unaddressed. While spontaneous closure of intraperitoneal cystotomies has been reported with simple catheter drainage,[69,70] a reliable closure mechanism will need

to be demonstrated before transvesical techniques can be applied in human subjects. Specific anatomic limitations of transurethral access include urethral length and diameter, which not only restricts the size and type of instrumentation that can be utilized, but also specimen extraction for extirpative procedures. The issue of urethral length has been overcome in traditional ureteroscopy with the use of ureteral access sheaths[71] and with rapidly developing technologies should not represent a significant hurdle to utilizing transvesical access for intra-abdominal procedures in the future. However, placement of larger instrumentation may require urethral dilation which would introduce risks of voiding dysfunction and incontinence which are currently unclear.[67]

Early porcine and human experiences

Two techniques have been described for obtaining transvesical intraperitoneal access. In unpublished ex vivo and in vivo porcine experiments, Gettman et al utilized a blunt tip prototype port as well as an injection needle followed by guidewire placement and balloon dilation. In their series of experiments, balloon dilation resulted in a larger cystotomy defect, but remained the preferred technique due to the force needed to gain entry with the blunt tip ports.[67] In the first published porcine model, Lima et al described transvesical endoscopic peritoneoscopy, liver biopsy, and falciform ligament division in eight female pigs (3 nonsurvival, 5 survival). In their experiment, a cystotomy was created using an open ended ureteral catheter under cystoscopic guidance. A 5.5 mm overtube was then placed over a guidewire to facilitate abdominal access, and a foley catheter was left in place for 4 days to facilitate spontaneous cystotomy closure. All survival animals recovered without complication, and at the time of necropsy animals all cystotomies were well healed and there were no signs of peritonitis or adhesions.[72] In subsequent work, Lima et al described a novel approach to perform transvesical and transdiaphragmatic endoscopic thoracoscopy. In six pigs, following transvesical access as described above, a ureteroscope was introduced through the left diaphragmatic dome into the left thoracic cavity to facilitate left pleural cavity visualization and perform lung biopsies. Similar to their previous experience, spontaneous closure of diaphragmatic and vesical access points were observed at post mortem examination with no attempt at mechanical closure and without subsequent complications.[73] Expanding these techniques to extirpative procedures, these authors reported a combined transgastric and transvesical port placement technique to perform cholecystectomies[74] as well as nephrectomies[61] in porcine models; however, difficulties with gastrotomy closure and specimen removal remain impediments to applicability in human trials.

Work in human subjects through a transvesical approach has been very limited. In unpublished work, Gettman et al discussed the feasibility of performing transvesical peritneoscopy, appendectomy, and division of the falciform ligament in two female unfrozen cadavers, maintaining a pneumoperitonem through the ureteroscope irrigation port.[67] In an extension of this work, Gettman et al reported the first human application of transvesical NOTES in a 56-year-old male undergoing robotic assisted laparoscopic prostatectomy for prostatic adenocarcinoma. Following standard port placement for prostatectomy and creation of pneumoperitoneum, a flexible injection needle was advanced through the bladder wall under simultaneous laparoscopic and cystoscopic vision. A balloon dilator was used to dilate the cystotomy and a flexible ureteroscope was placed over a guidewire to facilitate transvesical peritoneoscopy. Insufflation was maintained through the working channel of the ureteroscopy and all intraperitoneal structures were directly visualized from a pelvic position. Following removal of the ureteroscope, the cystotomy site was closed with figure of eight sutures using traditional robotic instruments prior to proceeding with the prostatectomy.[75] Transvesical access clearly has attractive advantages over other portals of entry including familiarity with access techniques, direct line of vision, and ability to maintain insufflation. However, clinical applications are hampered by technical limitations of contemporary equipment, lack of a reliable cystotomy closure mechanism, and the relative constraints of removing surgical specimens transurethrally.[67] It is likely that future technology will advance to the point that urethral diameter is no longer a significant limitation, but in the meantime the transvesical approach shows the most promise as a component of hybrid procedures in conjunction with either traditional umbilical laparoscopic ports pure NOTE procedures utilizing transgastric or transcolonic access.

Conclusions

Since the year 2000 there has been significant interest in the development and application of NOTES techniques for intra-abdominal surgery. From early porcine and human studies it is clear that limitations in instrumentation and reliable viscerotomy closure are limitations in the rapid adoption of true "minimally

invasive" techniques into contemporary clinical practice. For urologic application, transvaginal and transvesical NOTES appear to have the most utility for accessing the upper abdomen while minimizing the risk of peritoneal contamination, and early results using hybrid NOTES access with a transumbilical assistant port are both encouraging and exciting. As NOTES is still in its development, it is difficult to compare the safety and efficacy of early efforts with contemporary surgical interventions. It is evident that further development of these procedures and detailed prospective comparative studies are warranted before NOTES can be seriously considered for routine use in human subjects. There are currently three prospective human subject clinical trials investigating the application of NOTES to diagnostic peritoneoscopy, cholecystectomy, and foregut and urologic surgery.[8] Until findings of these studies are available, use in urologic and non-urologic surgery will likely be limited to hybrid procedures in specialty centers with considerable experience in these techniques. In the meantime, it is expected that technologic advances will be made to address the cumbersome equipment currently being utilized. Flexible endoscopes and devices designed to enable suturing, dissection, vessel ligation, anastamosis creation, and viscerotomy closure are sorely needed and are currently being investigated to facilitate intra-abdominal reconstructive procedures. While still in early development, with continued interest and dedicated research NOTES has the potential to change the face of minimally invasive surgery. □

References

1. Sauerland S, Lefering R, Neugebauer EA. Laparoscopic versus open surgery for suspected appendicitis. *Cochrane Database Syst Rev* 2004(4):CD001546.
2. McGee MF, Rosen MJ, Marks J, Onders RP, Chak A, Faulx A, Chen VK, Ponsky J. A primer on natural orifice transluminal endoscopic surgery: building a new paradigm. *Surg Innov* 2006;13(2):86-93.
3. Rattner D, Kalloo A. ASGE/SAGES Working Group on Natural Orifice Translumenal Endoscopic Surgery. October 2005. *Surg Endosc* 2006;20(2):329-333.
4. Rao GV. Transgastric appendectomy results and follow up (SAGES transgastric surgery panel). Presented at: SAGES meeting 2006.
5. Hochberger J, Lamade W. Transgastric surgery in the abdomen: the dawn of a new era? *Gastrointest Endosc* 2005;62(2):293-296.
6. Rao GV, Reddy DN, Banerjee R. NOTES: human experience. *Gastrointest Endosc Clin N Am* 2008;18(2):361-370.
7. Parsons JK, Varkarakis I, Rha KH, Jarrett TW, Pinto PA, Kavoussi LR. Complications of abdominal urologic laparoscopy: longitudinal five-year analysis. *Urology* 2004;63(1):27-32.
8. Flora ED, Wilson TG, Martin IJ, O'Rourke NA, Maddern GJ. A review of natural orifice translumenal endoscopic surgery (NOTES) for intra-abdominal surgery: experimental models, techniques, and applicability to the clinical setting. *Ann Surg* 2008;247(4):583-602.
9. Diamond E. Diagnostic culdoscopy in infertility: a study of 4,000 outpatient procedures. *J Reprod Med* 1978;21(1):23-30.
10. Gordts S, Watrelot A, Campo R, Brosens I. Risk and outcome of bowel injury during transvaginal pelvic endoscopy. *Fertil Steril* 2001;76(6):1238-1241.
11. Box GN, Bessler M, Clayman RV. Transvaginal access: current experience and potential implications for urologic applications. *J Endourol* 2009;23(5):753-757.
12. Tsin DA, Sequeria RJ, Giannikas G. Culdolaparoscopic cholecystectomy during vaginal hysterectomy. *JSLS* 2003;7(2):171-172.
13. Gill IS, Cherullo EE, Meraney AM, Borsuk F, Murphy DP, Falcone T. Vaginal extraction of the intact specimen following laparoscopic radical nephrectomy. *J Urol* 2002;167(1):238-241.
14. Breda G, Silvestre P, Giunta A, Xausa D, Tamai A, Gherardi L. Laparoscopic nephrectomy with vaginal delivery of the intact kidney. *Eur Urol* 1993;24(1):116-117.
15. Lin VC, Lu K. Laparoscopic complete urinary tract exenteration with the specimen withdrawn transvaginally. *BJU Int* 2009;103(11):1584; author reply:1584-1585.
16. Chang WC, Huang SC, Sheu BC, Chen CL, Torng PL, Hsu WC, Chang DY. Transvaginal hysterectomy or laparoscopically assisted vaginal hysterectomy for nonprolapsed uteri. *Obstet Gynecol* 2005;106(2):321-326.
17. Su HY, Ding DC, Chen DC, Lu MF, Liu JY, Chang FY. Prospective randomized comparison of single-dose versus 1-day cefazolin for prophylaxis in gynecologic surgery. *Acta Obstet Gynecol Scand* 2005;84(4):384-389.
18. Korn AP, Grullon K, Hessol N, Lin P, Siopak J. Does vaginal cuff closure decrease the infectious morbidity associated with abdominal hysterectomy? *J Am Coll Surg* 1997;185(4):404-407.
19. Gettman MT, Lotan Y, Napper CA, Cadeddu JA. Transvaginal laparoscopic nephrectomy: development and feasibility in the porcine model. *Urology* 2002;59(3):446-450.
20. Clayman RV, Box GN, Abraham JB, Lee HJ, Deane LA, Sargent ER, Nguyen NT, Chang K, Tan AK, Ponsky LE, McDougall DM. Rapid communication: transvaginal single-port NOTES nephrectomy: initial laboratory experience. *J Endourol* 2007; 21(6):640-644.
21. Raman JD, Bergs RA, Fernandez R, Bagrodia A, Scott DJ, Tang SJ, Pearle MS, Cadeddu JA. Complete transvaginal NOTES nephrectomy using magnetically anchored instrumentation. *J Endourol* 2009;23(3):367-371.
22. Scott DJ, Tang SJ, Fernandez R, Bergs R, Goova MT, Zeltser I, Kehdy FJ, Cadeddu JA. Completely transvaginal NOTES cholecystectomy using magnetically anchored instruments. *Surg Endosc* 2007;21(12):2308-2316.
23. Perretta S, Allemann P, Asakuma M, Cahill R, Dallemagne B, Marescaux J. Feasibility of right and left transvaginal retroperitoneal nephrectomy: from the porcine to the cadaver model. *J Endourol* 2009;23(11):1887-1892.
24. Perretta S, Allemann P, Asakuma M, Dallemagne B, Marescaux J. Adrenalectomy using natural orifice translumenal endoscopic surgery (NOTES): a transvaginal retroperitoneal approach. *Surg Endosc* 2009;23(6):1390.
25. Isariyawongse JP, McGee MF, Rosen MJ, Cherullo EE, Ponsky LE. Pure natural orifice transluminal endoscopic surgery (NOTES) nephrectomy using standard laparoscopic instruments in the porcine model. *J Endourol* 2008;22(5):1087-1091.
26. Haber GP, Brethauer S, Crouzet S, Berger A, Gatmaitan P, Kamoi K, Gill I. Pure 'natural orifice transluminal endoscopic surgery' for transvaginal nephrectomy in the porcine model. *BJU Int* 2009;104(9):1260-1264.

27. Crouzet S, Haber GP, Kamoi K, Berger A, Brethauer S, Gatmaitan P, Gill IS, Kaouk JH. Natural orifice translumenal endoscopic surgery (NOTES) renal cryoablation in a porcine model. *BJU Int* 2008;102(11):1715-1718.
28. Box GN, Lee HJ, Santos RJ, Abraham JB, Louie MK, Gamboa AJ, Alipanah R, Deane LA, McDougall EM, Clayman RV. Rapid communication: robot-assisted NOTES nephrectomy: initial report. *J Endourol* 2008;22(3):503-506.
29. Haber GP, Crouzet S, Kamoi K, Berger A, Aron M, Goel R, Canes D, Desai M, Gill IS, Kaouk JH. Robotic NOTES (Natural Orifice Translumenal Endoscopic Surgery) in reconstructive urology: initial laboratory experience. *Urology* 2008;71(6):996-1000.
30. Bessler M, Stevens PD, Milone L, Parikh M, Fowler D. Transvaginal laparoscopically assisted endoscopic cholecystectomy: a hybrid approach to natural orifice surgery. *Gastrointest Endosc* 2007;66(6):1243-1245.
31. Zornig C, Emmermann A, von Waldenfels HA, Mofid H. Laparoscopic cholecystectomy without visible scar: combined transvaginal and transumbilical approach. *Endoscopy* 2007;39(10):913-915.
32. Davila F, Tsin DA, Dominguez G, Davila U, Jesus R, Gomez de Arteche A. Transvaginal cholecystectomy without abdominal ports. *JSLS* 2009;13(2):213-216.
33. Branco AW, Branco Filho AJ, Kondo W, Noda RW, Kawahara N, Camargo AA, Stunitz LC, Valente J, Rangel M. Hybrid transvaginal nephrectomy. *Eur Urol* 2008;53(6):1290-1294.
34. Kaouk JH, White WM, Goel RK, Brethauer S, Crouzet S, Rackley RR, Moore C, Ingber MS, Haber GP. NOTES transvaginal nephrectomy: first human experience. *Urology* 2009;74(1): 5-8.
35. Sotelo R, de Andrade R, Fernandez G, Ramirez D, Di Grazia E, Carmona O, Moreira O, Berger A, Aron M, Desai MM, Gill IS. NOTES hybrid transvaginal radical nephrectomy for tumor: stepwise progression toward a first successful clinical case. *Eur Urol* 2010;57(1):138-144.
36. Figueiredo FA, da Costa MC, Pelosi AD, Martins RN, Machado L, Francioni E. Predicting outcomes and complications of percutaneous endoscopic gastrostomy. *Endoscopy* 2007;39(4): 333-338.
37. Xavier K, Gupta M, Landman J. Transgastric NOTES: Current experience and potential implications for urologic applications. *J Endourol* 2009;23(5):737-741.
38. Jagannath SB, Kantsevoy SV, Vaughn CA, Chung SS, Cotton PB, Gostout CJ, Hawes RH, Pasricha PJ, Scorpio DG, Magee CA, Pipitone LJ, Kalloo AN. Peroral transgastric endoscopic ligation of fallopian tubes with long-term survival in a porcine model. *Gastrointest Endosc* 2005;61(3):449-453.
39. Kalloo AN, Singh VK, Jagannath SB, Niiyama H, Hill SL, Vaughn CA, Magee CA, Kantsevoy SV. Flexible transgastric peritoneoscopy: a novel approach to diagnostic and therapeutic interventions in the peritoneal cavity. *Gastrointest Endosc* 2004;60(1):114-117.
40. Sumiyama K, Gostout CJ, Gettman MT. Status of access and closure techniques for NOTES. *J Endourol* 2009;23(5):765-771.
41. Pai RD, Fong DG, Bundga ME, Odze RD, Rattner DW, Thompson CC. Transcolonic endoscopic cholecystectomy: a NOTES survival study in a porcine model (with video). *Gastrointest Endosc* 2006;64(3):428-434.
42. Swanstrom LL, Kozarek R, Pasricha PJ, Gross S, Birkett D, Park PO, Saadat V, Ewers R, Swain P. Development of a new access device for transgastric surgery. *J Gastrointest Surg* 2005;9(8):1129-1136; discussion 1136-1127.
43. Ikeda K, Fritscher-Ravens A, Mosse CA, Mills T, Tajiri H, Swain CP. Endoscopic full-thickness resection with sutured closure in a porcine model. *Gastrointest Endosc* 2005;62(1):122-129.
44. Sumiyama K, Gostout CJ. Novel techniques and instrumentation for EMR, ESD, and full-thickness endoscopic luminal resection. *Gastrointest Endosc Clin N Am* 2007;17(3):471-485, v-vi.
45. Swain P, Park PO, Mills T. Bard EndoCinch: the device, the technique, and pre-clinical studies. *Gastrointest Endosc Clin NAm* 2003;13(1):75-88.
46. Hu B, Chung SC, Sun LC, Lau JY, Kawashima K, Yamamoto T, Cotton PB, Gostout CJ, Hawes RH, Kalloo AN, Kantsevoy SV, Pasricha PJ. Endoscopic suturing without extracorporeal knots: a laboratory study. *Gastrointest Endosc* 2005;62(2):230-233.
47. Magno P, Giday SA, Dray X, Chung SS, Cotton PB, Gostout CJ, Hawes RH, Kalloo AN, Pasricha PJ, White JJ, Assumpcao L, Marohn MR, Gabrielson KL, Kantsevoy SV. A new stapler-based full-thickness transgastric access closure: results from an animal pilot trial. *Endoscopy* 2007;39(10):876-880.
48. McGee MF, Marks JM, Onders RP, Chak A, Rosen MJ, Williams CP, Jin J, Schomisch SJ, Ponsky JL. Infectious implications in the porcine model of natural orifice transluminal endoscopic surgery (NOTES) with PEG-tube closure: a quantitative bacteriologic study. *Gastrointest Endosc* 2008;68(2):310-318.
49. Dray X, Giday SA, Buscaglia JM, Gabrielson KL, Kantsevoy SV, Magno P, Assumpcao L, Shin EJ, Reddings SK, Woods KE, Marohn MR, Kalloo AN. Omentoplasty for gastrotomy closure after natural orifice transluminal endoscopic surgery procedures (with video). *Gastrointest Endosc* 2009;70(1):131-140.
50. Sclabas GM, Swain P, Swanstrom LL. Endoluminal methods for gastrotomy closure in natural orifice transenteric surgery (NOTES). *Surg Innov* 2006;13(1):23-30.
51. Kantsevoy SV, Jagannath SB, Niiyama H, Chung SS, Cotton PB, Gostout CJ, Hawes RH, Pasricha PJ, Magee CA, Vaughn CA, Barlow D, Shimonaka H, Kalloo AN. Endoscopic gastrojejunostomy with survival in a porcine model. *Gastrointest Endosc* 2005;62(2):287-292.
52. Fritscher-Ravens A, Mosse CA, Ikeda K, Swain P. Endoscopic transgastric lymphadenectomy by using EUS for selection and guidance. *Gastrointest Endosc* 2006;63(2):302-306.
53. Merrifield BF, Wagh MS, Thompson CC. Peroral transgastric organ resection: a feasibility study in pigs. *Gastrointest Endosc* 2006; 63(4):693-697.
54. Wagh MS, Merrifield BF, Thompson CC. Survival studies after endoscopic transgastric oophorectomy and tubectomy in a porcine model. *Gastrointest Endosc* 2006;63(3):473-478.
55. Park PO, Bergstrom M, Ikeda K, Fritscher-Ravens A, Swain P. Experimental studies of transgastric gallbladder surgery: cholecystectomy and cholecystogastric anastomosis (videos). *Gastrointest Endosc* 2005;61(4):601-606.
56. Sumiyama K, Gostout CJ, Rajan E, Bakken TA, Deters JL, Knipschield MA, Hawes RH, Kalloo AN, Pasricha PJ, Chung S, Kantsevoy SV, Cotton PB. Pilot study of the porcine uterine horn as an in vivo appendicitis model for development of endoscopic transgastric appendectomy. *Gastrointest Endosc* 2006;64(5):808-812.
57. Kantsevoy SV, Hu B, Jagannath SB, Vaughn CA, Beitler DM, Chung SS, Cotton PB, Gostout CJ, Hawes RH, Pasricha PJ, Magee CA, Pipitone LJ, Talamini MA, Kalloo AN. Transgastric endoscopic splenectomy: is it possible? *Surg Endosc* 2006;20(3): 522-525.
58. Hazey JW, Narula VK, Renton DB, Reavis KM, Paul CM, Hinshaw KE, Muscarella P, Ellison EC, Melvin WS. Natural-orifice transgastric endoscopic peritoneoscopy in humans: Initial clinical trial. *Surg Endosc* 2008;22(1):16-20.
59. Marks JM, Ponsky JL, Pearl JP, McGee MF. PEG «Rescue»: a practical NOTES technique. *Surg Endosc* 2007;21(5):816-819.
60. Asakuma M, Perretta S, Allemann P, Cahill R, Con SA, Solano C, Pasupathy S, Mutter D, Dallemagne B, Marescaux J. Challenges and lessons learned from NOTES cholecystectomy initial experience: a stepwise approach from the laboratory to clinical application. *J Hepatobiliary Pancreat Surg* 2009;16(3):249-254.
61. Lima E, Rolanda C, Pego JM, Henriques-Coelho T, Silva D, Osorio L, Moreira I, Carvalho JL, Correia-Pinto J. Third-generation nephrectomy by natural orifice transluminal endoscopic surgery. *J Urol* 2007;178(6):2648-2654.

62. Shin EJ, Kalloo AN. Transcolonic NOTES: Current experience and potential implications for urologic applications. *J Endourol* 2009; 23(5):743-746.
63. Bachman SL, Sporn E, Furrer JL, Astudillo JA, Calaluce R, McIntosh MA, Miedema BW, Thaler K. Colonic sterilization for natural orifice translumenal endoscopic surgery (NOTES) procedures: a comparison of two decontamination protocols. *Surg Endosc* 2009;23(8):1854-1859.
64. Fong DG, Pai RD, Thompson CC. Transcolonic endoscopic abdominal exploration: a NOTES survival study in a porcine model. *Gastrointest Endosc* 2007;65(2):312-318.
65. Ryou M, Fong DG, Pai RD, Tavakkolizadeh A, Rattner DW, Thompson CC. Dual-port distal pancreatectomy using a prototype endoscope and endoscopic stapler: a natural orifice transluminal endoscopic surgery (NOTES) survival study in a porcine model. *Endoscopy* 2007;39(10):881-887.
66. Wilhelm D, Meining A, von Delius S, Fiolka A, Can S, Hann von Weyhern C, Schneider A, Feussner H. An innovative, safe and sterile sigmoid access (ISSA) for NOTES. *Endoscopy* 2007; 39(5):401-406.
67. Granberg CF, Frank I, Gettman MT. Transvesical NOTES: Current experience and potential implications for urologic applications. *J Endourol* 2009;23(5):747-752.
68. Aron M, Haber GP, Desai MM, Gill IS. Flexible robotics: a new paradigm. *Curr Opin Urol* 2007;17(3):151-155.
69. Alperin M, Mantia-Smaldone G, Sagan ER. Conservative management of postoperatively diagnosed cystotomy. *Urology* 2009;73(5):1163 e1117-1169.
70. Macejko AM, Pazona JF, Loeb S, Kimm S, Nadler RB. Management of distal ureter in laparoscopic nephroureterectomy--a comprehensive review of techniques. *Urology* 2008;72(5):974-981.
71. Stern JM, Yiee J, Park S. Safety and efficacy of ureteral access sheaths. *J Endourol* 2007;21(2):119-123.
72. Lima E, Rolanda C, Pego JM, Henriques-Coelho T, Silva D, Carvalho JL, Correia-Pinto J. Transvesical endoscopic peritoneoscopy: a novel 5 mm port for intra-abdominal scarless surgery. *J Urol* 2006;176(2):802-805.
73. Lima E, Henriques-Coelho T, Rolanda C, Pego JM, Silva D, Carvalho JL, Correia-Pinto J. Transvesical thoracoscopy: a natural orifice translumenal endoscopic approach for thoracic surgery. *Surg Endosc* 2007;21(6):854-858.
74. Rolanda C, Lima E, Pego JM, Henriques-Coelho T, Silva D, Moreira I, Macedo G, Carvalho JL, Correia-Pinto J. Third-generation cholecystectomy by natural orifices: transgastric and transvesical combined approach (with video). *Gastrointest Endosc* 2007;65(1):111-117.
75. Gettman MT, Blute ML. Transvesical peritoneoscopy: initial clinical evaluation of the bladder as a portal for natural orifice translumenal endoscopic surgery. *Mayo Clin Proc* 2007;82(7):843-845.