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Natural Orifice Translumenal Endoscopic Surgery: A Critical Review

Jonathan P. Pearl · Jeffrey L. Ponsky

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Abstract Natural orifice translumenal endoscopic surgery (NOTES) involves the intentional puncture of one of the viscera (e.g., stomach, rectum, vagina, urinary bladder) with an endoscope to access the abdominal cavity and perform an intraabdominal operation. Early laboratory work focused on feasibility studies, including such accomplishments as pure transgastric splenectomy and gastrojejunostomy. Contemporary laboratory work is investigating the infectious and immunologic implications of NOTES and honing the tools and techniques required for complex abdominal operations. Today NOTES has entered the clinical arena in a few cases: the first clinical series of transgastric peritoneoscopy has recently been published; multiple groups are accumulating patients in studies of NOTES cholecystectomy, either via the transgastric or transvaginal route; and a series of transgastric appendectomies has been well publicized, yet it remains unpublished. Although clinical NOTES is gaining momentum, the field should remain in check while rigorous laboratory work is performed and cogent clinical trials are undertaken. The zeal for NOTES should not take precedence over the welfare of the patient.

Keywords Endoscopic surgery · Intraabdominal · Translumenal · Peritoneoscopy · Cholecystectomy

Since Kalloo's publication of transgastic peritoneoscopy in 2004[1] the field of natural orifice translumenal endoscopic surgery (NOTES) has evolved from the ethereal to the tangible. In a brief time period, NOTES has been shown to be feasible in numerous laboratory animal studies and NOTES-specific instrumentation has entered the research and development stages (Fig. 1). Furthermore, rigorous laboratory research into the infectious and immunologic impact of NOTES has, in many cases, shown the equivalence of NOTES to laparoscopy and conventional abdominal surgery. Today careful clinical trials of NOTES peritoneoscopy and cholecystectomy are being conducted. As the data accumulate and instrumentation improves, NOTES may play a role in the future of abdominal surgery.

J. P. Pearl
Department of Surgery, National Naval Medical Center,
Bethesda, MD, USA

J. L. Ponsky (✉)
Department of Surgery,
Case Western Reserve University School of Medicine,
11100 Euclid Ave,
Cleveland, OH 44106, USA
e-mail: jponsky@yahoo.com

The Fundamentals

The central tenets of NOTES consist of passage of a flexible endoscope through one of the body's natural orifices, perforation of a viscus, and performance of abdominal surgery using endoscopic visualization. The endoscope may be inserted through the mouth, anus, urethra, or vagina with puncture of the stomach (the esophagus for mediastinal exploration), rectum, urinary bladder, or vagina, respectively.

Although precise details of NOTES procedures vary between centers, most groups adhere to the same general principles. For transgastric surgery, a standard gastroscope is passed through the mouth into the stomach. A small anterior gastrotomy is made, typically with an endoscopic needleknife. A wire is passed through the site into the abdominal cavity, and then the tract is enlarged with an endoscopic dilating balloon to accommodate the endo-

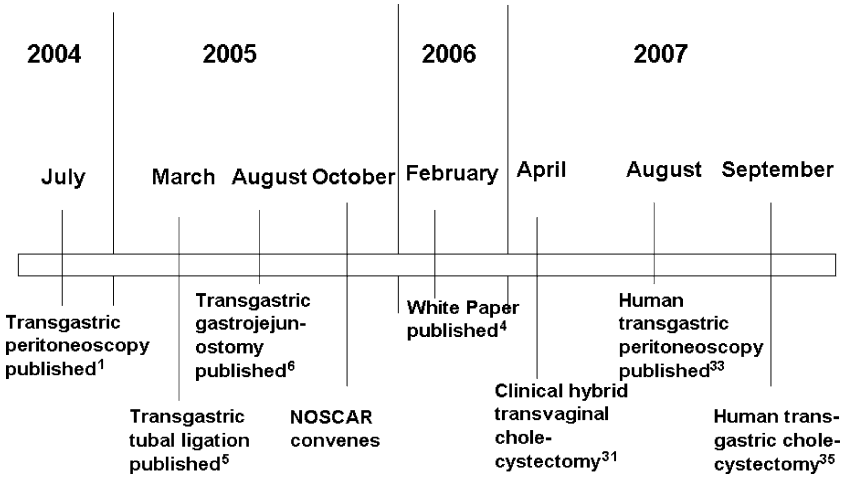

Figure 1 Timeline of significant achievements in the field of NOTES. In a compressed time period NOTES has progressed from laboratory work to meaningful clinical studies.

scope. Transcolonic and transvesical operations use similar methods for entering the peritoneal cavity.

Once the endoscope in advanced into the abdominal cavity, a pneumoperitoneum is generated using endoscopic insufflation. The scope is maneuvered to view the organ of interest. Standard endoscopic instruments, such as biopsy forceps and polypectomy snares, are then passed through the working channels and used for tissue manipulation. When the operation is completed, the endoscope is returned to the lumen of this viscus and the viscerotomy is closed.

Shortcomings of Contemporary Techniques

From the description above, many limitations of current NOTES techniques are evident. Foremost is the fact that a hole is intentionally made in one of the viscera, which repudiates decades of surgical dogma. The patient might be susceptible to infectious and immunologic consequences that are not present in laparoscopy and conventional surgery.

The inherent flexibility of the endoscope impedes achieving a stable operating field. During transgastric surgery, a deep loop into the pelvis might be required to view the right upper quadrant, for example, and the endoscope might resist this positioning. Because of retroflexion, the endoscopic image might be inverted or reversed, further complicating the operation.

The current unavailability of adequate instrumentation restricts the ability to perform meticulous dissection in NOTES. In-line endoscopic tools have a restricted range of motion and limited degrees of freedom. There is not widespread availability of endoscopic scissors and graspers, which would be critical for retraction and dissection. In addition, in-line instrumentation and optics do not allow triangulation of the visual field and instruments, a concept found to be critical in laparoscopy.

As a purposeful viscerotomy is made in NOTES, its secure closure is imperative to ensure the safety of the operation. Initial laboratory work managed the viscerotomy without closure or by occlusion using a percutaneous endoscopic gastrostomy (PEG)-type gastrostomy tube.[2] Both methods were fraught with high rates of intra-abdominal contamination in the porcine model. Thus, more reliable methods that achieve full-thickness closure of the viscerotomy are currently being investigated.

Advantages of NOTES

Some critics are disenchanted with NOTES, given its dissonance with conventional surgical teaching. However, advances are being made in mitigating some of the current shortcomings of NOTES. To that end, there may be some benefits of natural orifice surgery that make its pursuit rewarding.

The immunologic impact of NOTES may be favorable for the patient. A recent laboratory study from Case Western Reserve University showed lower levels of tumor necrosis factor-α (TNF-α) after NOTES peritoneoscopy compared to laparoscopic abdominal exploration and laparotomy.[3] NOTES may lead to less impairment of the peritoneal immune system and possibly even improved oncologic and infectious outcomes.

Natural orifice surgery may decrease the degree of abdominal adhesion formation. Much like laparoscopy, the minimal access nature of NOTES might diminish the stimuli for adhesions and, subsequently, reduce the incidence of postoperative bowel obstruction or simplify future abdominal operations.

NOTES can likely be performed without the need for general anesthesia. As no skin incision is made, the requirement for analgesia might be satisfied with conscious sedation. Therefore, NOTES could be performed in the

intensive care unit or endoscopy suite, rather than a standard operating room.

The NOTES team and its equipment are portable. A single endoscopy tower houses all of the necessary equipment. Furthermore, most NOTES procedures are performed without sterile instruments, but with scopes subjected to high-level disinfection. This makes NOTES amenable to austere environments, such as battlefields and developing countries, where sterilization equipment is not available.

Finally, the esthetic benefits of NOTES. The public at large has become captivated with the concept of "no-scar" abdominal operations. This is feasible with pure NOTES cases, although esthetics should not be the driving force behind NOTES.

NOSCAR: An Influential Organization

The initial enthusiasm for "no-scar" abdominal surgery, coupled with the limitations of NOTES techniques, could have resulted in premature clinical applications of natural orifice surgery. So that the field of NOTES did not proceed unfettered, a new organization was formed: Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR). In a collaborative effort, members of the American Society for Gastrointestinal Endoscopy and the Society of American Gastrointestinal Endoscopic Surgeons joined to form NOSCAR. The purpose of this organization is to regulate the progress of NOTES and ensure the safety of clinical applications.

An influential treatise from NOSCAR has been deemed the "White Paper,"[4] which delineates the guidelines for laboratory and clinical natural orifice surgery. In the White Paper, the authors outlined the current shortcomings of NOTES techniques and some of the potential solutions. A call for rigorous scientific research was sounded before clinical employment of NOTES. Finally, and perhaps most importantly, cooperation between the fields of gastroenterology and surgery was mandated, ensuring the liberal communication of research findings and the multidisciplinary makeup of NOTES teams.

Recently, NOSCAR launched a comprehensive NOTES database. All patients throughout the world who are enrolled in NOTES trials will be entered into the database. This fosters sharing of information and engenders a sense of full disclosure.

Laboratory Achievements to Date

The seminal publication by Kalloo and colleagues led to the organization of the Apollo group. Shortly after the publication of transgastric peritoneoscopy, the Apollo group published reports on transgastric tubal ligation,[5] gastrojejunostomy,[6] and splenectomy[7] in a porcine model. Recently, members of the Apollo Group collaborated in the performance of peroral transgastric ventral hernia repairs in a porcine model. These publications were significant in that complex operations were shown to be feasible using NOTES techniques and the animals survived without undue complications.

Many teams followed the Apollo Group's lead and performed animal feasibility studies. Transgastric appendectomy,[8] cholecystectomy,[9] and oopherectomy[10] were performed. The transcolonic[9] approach has been used to perform cholecystectomy, and the transvaginal approach has been used in laboratory animals to perform nephrectomy.[11] Combined transrectal and transgastric approaches allow performance of complex small bowel resections with intracorporeal formation of anastomoses.[12]

Much of the initial laboratory research focused on the feasibility of NOTES. Although plagued with restrictions, practically any abdominal operation could be performed using the available natural orifice techniques. As outlined in the White Paper, the more poignant questions concerned the infectious and immunologic implications of natural orifice surgery.

Reliable closure of the viscerotomy is the critical step in avoiding intraabdominal infection. As mentioned above, leaving the viscerotomy open and PEG tube occlusion of the gastrotomy were shown to be inadequate in the porcine model. Endoscopic clips, as might be used in a bleeding vessel, have also been used with some success.[13] However, clips only provide mucosal approximation, and a full-thickness closure comports with proven surgical principles.

Numerous devices have been used to attempt full-thickness closure. One such instrument is the NDO Plicator. This device was initially developed for the endoscopic management of gastroesophageal reflux disease. It is a 15-mm instrument whose jaws place a full-thickness permanent suture with polytetrafluoroethylene bolsters. A 6-mm endoscope is advanced through the working channel of the scope to provide visualization. In addition, a patented retracting device permits grasping of tissue and more accurate placement of sutures.

Closure of full-thickness gastrotomies has been shown to be reliable with the NDO Plicator.[14,15] Bursting pressures of the porcine stomach after closure exceed 90 mmHg and a water-tight closure is achieved, as evidenced by fluoroscopic contrast studies. Survival studies in laboratory animals have shown minimal rates of intraabdominal infections after transgastric peritoneoscopy and closure with the NDO Plicator.

Another group has developed a method of gastrotomy closure using a commercially available overtube and

suturing device.[16] The overtube is steerable, torque-stable, fixable, and accommodates a slim endoscope and a suturing device. The suturing device consists of a grasper that locks at 45 degrees relative to the instrument shaft. A needle and suture passes through the device and can be bolstered with polyester tissue anchors. In the porcine stomach, robust, full-thickness sutures and fine tissue manipulation was achievable using this platform.

A method of translumenal access has been developed by the Penn State group that might obviate the need for full-thickness closure, deemed the self-approximating translumenal access technique (STAT).[17,18] An incision is first made in the gastric mucosa. The submucosal space is developed and a tunnel of at least 5 cm length is created using a dissecting balloon. After tunneling away from the mucosal defect, the muscularis and serosa are punctured, and the abdomen is entered. After the abdominal portion of the operation, the scope is withdrawn and only the mucosa is closed. In a porcine model, this technique has yielded favorable results.

Sumiyama and colleagues have performed transgastric cholecystectomies in laboratory animals using an offset gastrostomy, similar to STAT, to access the abdominal cavity. A submucosal tunnel was created using high-pressure carbon dioxide followed by a myotomy to puncture the remaining gastric wall. The endoscope was advanced through the tunnel into the peritoneal cavity and a cholecystectomy was performed. The submucosal plane was angled cephalad to position the endoscope for operating in the right upper quadrant. At the conclusion of the operation, the mucosal entry point was closed with endoscopic clips or tissue anchors. The animals that survived the operation were followed for 1 week and then sacrificed.

In animal studies, the Ohio State group has closed gastrotomies with a bioabsorbable plug, such as might be employed in inguinal hernia repair.[19,20] This eliminated the need for complex tissue manipulation and provided water-tight closure with minimal infectious complications. This technique might simplify the process of viscerotomy closure, provided that it is as reliable as a full-thickness tissue approximation.

The pneumoperitoneum from NOTES is commonly created using endoscopic insufflation. As in laparoscopy, the intraabdominal pressure requires continuous monitoring during NOTES. Unchecked insufflation might lead to abdominal compartment syndrome. A recent study has shown that pressure transducers fitted to the end of a gastroscope or passed through a working channel detect intraabdominal pressure with a high degree of correlation with actual intraabdominal pressure.[21] Such devices could be easily incorporated into NOTES operating endoscopes. Alternative means to monitor intraabdominal pressure include passage of a transabdominal Verees needle or other similar transabdominal catheter.

Adequate retraction is imperative to safely perform complex abdominal operations, such as cholecystectomy. Given the nature of endoscopic instruments, appropriate retraction has been difficult to achieve. The group from the University of Texas-Southwestern has developed a clever method using intraabdominal magnets to provide retraction during NOTES procedures.[22,23] In their technique, an extraabdominal magnet is paired to its intraabdominal counterpart. The organ of interest is affixed with a metal device, such as a clip, and coupled to the magnet. Tissue manipulation is performed by moving the external component of the magnet to achieve the desired retraction.

To provide a stable operating platform for natural orifice surgery, new endoscopes are under development. Swanstrom[24] and others[16] are using endoscopes that allow the surgeon to operate with both hands, rather than using one hand to stabilize the endoscope. Others[25] are using commercially made multibending endoscopes with dual instrument channels to provide better maneuverability and stability. The NOTES endoscope of the future might have the ability to maintain a fixed position and its multiple working channels could be offset from the optics so as to provide for triangulation.

Some groups have overcome the obstacles of triangulation and retraction by inserting multiple endoscopes into the abdomen. The group from the University of California-San Diego has performed complex small bowel resections by inserting endoscopes and staplers through both the stomach and rectum.[12,26] While these procedures were done under laparoscopic supervision, the lessons learned from the dual-scope technique might be applied to pure NOTES cases.

Recently, laboratory NOTES sigmoid colectomy has been performed without a flexible endoscope. Swanstrom and colleagues used transanal endoscopic microsurgery techniques to perform a radical sigmoid colectomy.[27] Human cadavers were used in performing the sigmoid resection with high ligation of the vessels and generous lymphadenectomy.

Clinical NOTES

Some might suggest that natural orifice surgery has been practiced for years. Translumenal drainage of pancreatic pseudocysts[28] and transgastric pancreatic debridement[29] are considered standard procedures for many advanced endoscopists. Culdoscopy, in which a laparoscope is inserted into the abdomen through the vagina, is commonly used in the management of infertility and sometimes employed for tubal ligation. Some might even note that percutaneous endoscopic gastrostomy, first described in 1979,[30] was the

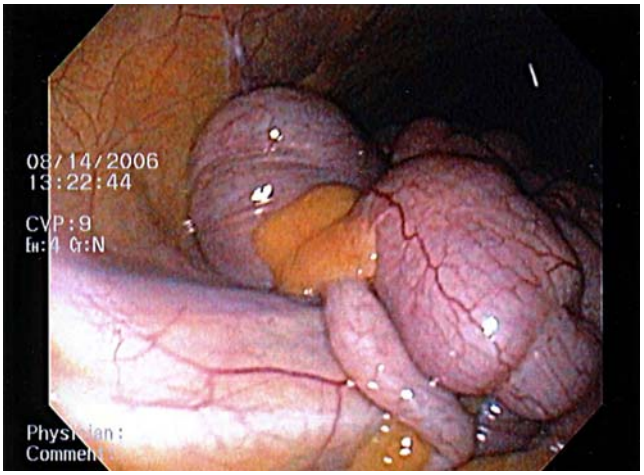

Figure 2 View of the appendix from a transgastric endoscopic approach.

first endoscopic procedure that purposely breached the gastric lumen and supplanted a standard operation, thus qualifying as NOTES.

The first case of contemporary natural orifice surgery was performed nearly a decade ago by a surgeon practicing in the United States. A hybrid laparoscopic/endoscopic cholecystectomy was undertaken. Needlescopic instruments were used to perform a laparoscopic cholecystectomy using standard techniques. An anterior gastrotomy was made and the specimen was placed into the stomach and removed by mouth with the endoscope. The gastrotomy was then closed using intracorporeal suturing techniques.

After the first unpublished hybrid case, natural orifice techniques went largely ignored until Kalloo's 2004 publication. After the successes of the Apollo group with laboratory natural orifice surgery, a group in India performed a series of transgastric appendectomies and transgastric tubal ligations (Fig. 2). Although unpublished, the videos have been widely disseminated at meetings across the world. The series has accumulated at least 12 patients, reportedly with salutary results.

A recent hybrid procedure generated a great deal of publicity in the lay press and at surgical meetings. The Columbia group in New York City performed a hybrid cholecystectomy with extraction of the specimen through the vagina.[31,32] Dissection and retraction were performed with both the laparoscopic and endoscopic instruments. The patient, a middle-aged woman, reportedly recovered well after this procedure without complications.

Additional cases of hybrid cholecystectomy have circulated across the world (Fig. 3). From France to Brazil to Peru, anecdotal case series of hybrid cholecystectomy, using a variety of techniques, have been publicized at international surgery and gastroenterology meetings.

The Ohio State group has performed the first institutional review board-approved series of hybrid transgastric peritoneoscopy.[33] NOTES peritoneoscopy was performed in all patients with suspected adenocarcinoma in the head of the pancreas. An initial diagnostic laparoscopy was performed followed by the creation of an anterior gastrotomy and transgastric peritoneoscopy under laparoscopic supervision. In most cases, NOTES abdominal exploration was found to be equivalent to laparoscopy in detecting peritoneal metastases or other unresectable disease. There were no complications directly related to the transgastric procedure. The authors concluded that transgastric peritoneoscopy in humans is feasible and safe.

Perhaps the first case of pure NOTES published from the United States was completed at Case Western Reserve University in Cleveland.[34] A PEG tube placed for nutritional support was dislodged 3 days after its initial placement. The stomach had not yet adhered to the anterior gastric wall, therefore there was a free communication between the gastric lumen and the abdomen. The abdomen was explored and irrigated, and the gastrostomy tube was restored using pure NOTES techniques.

To rescue the PEG without laparotomy or laparoscopy, a gastroscope was advanced into the stomach with identification of the prior gastrotomy site. The aperture was dilated with a balloon and the endoscope advanced into the abdominal cavity. Some soilage was identified, which was cleansed using the endoscopic irrigation channel. The prior abdominal incision was used to pass a wire into the peritoneal cavity, and the PEG was restored using the pull technique. After the "PEG Rescue" the patient recovered well, without evidence of intraabdominal infection.

The first purely translumenal cholecystectomy was reported by Marescaux and colleagues from Strasbourg, France.[35] The transvaginal route was used to access the abdomen in a 30-year-old woman with symptomatic cholelithiasis. A 2-mm needleport was used for insufflation

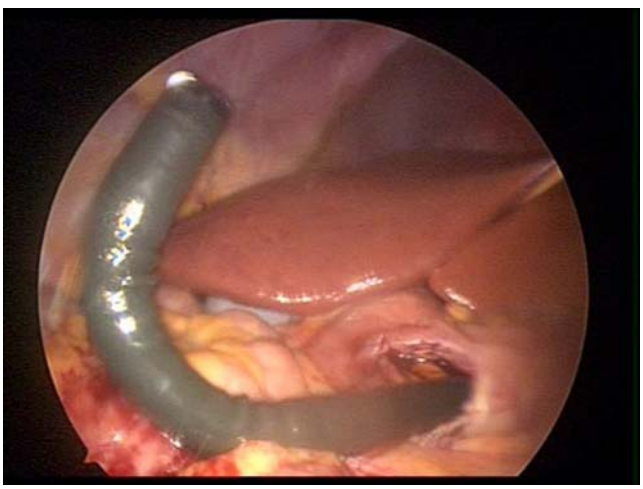

Figure 3 Laparoscopic view of the transgastric approach to the right upper quadrant. To visualize the gallbladder, the endoscope typically requires a deep loop into the peritoneum.

and monitoring of intraabdominal pressure. The cholecystectomy was performed without the aid of a laparoscope using only NOTES techniques. The patient's recovery was uneventful.

NOTES: The Domain of Surgeons or Gastroenterologists?

The question arises as to whether surgeons or gastroenterologists will be the primary practitioners of NOTES.[36,37] After all, abdominal operations are typically under the purview of the general surgeon, but gastroenterologists are usually expert in flexible endoscopy. In all likelihood, a small subset of endoscopic surgeons and advanced gastrointestinal endoscopists will be the NOTES surgeons of the future.

The NOTES surgeon should be expert in flexible endoscopy, abdominal anatomy, and surgical technique. He or she should be facile in managing the pre- and postoperative care of the patients and, in particular, should be capable of handling complications from the procedure. Many would argue that NOTES surgeons should be able to perform an operation laparoscopically and conventionally, as conversion to one of these modalities is a possibility in any NOTES procedure.

Those qualifications transcend the boundaries of most general surgery and gastrointestinal endoscopy teaching programs; hence, a new training model will likely be adopted. A gastrointestinal surgeon wishing to practice NOTES will likely pursue fellowship training in advanced endoscopy. A gastroenterologist might complete a year of advanced interventional endoscopy and possibly an additional year dedicated to NOTES. Trainees from both the fields of surgery and gastroenterology should dedicate a substantial amount of time to laboratory endeavors, as this is where skills can be safely honed before clinical application.

By necessity, training for a future in NOTES surgery will be different for surgeons and gastroenterologists. A gastrointestinal surgeon will likely focus on the technical aspects of flexible endoscopy, and a gastroenterologist might need familiarization with gross abdominal anatomy and laparoscopy.

Neither surgeons nor gastroenterologists should consider NOTES an infringement on their territory or the demise of traditional surgery or endoscopy. In the near term, NOTES will be practiced by only a small proportion of surgeons and gastroenterologists with a limited number of indications. Most cases will likely be performed at specialized tertiary centers with expertise in the field, and gastrointestinal surgery and endoscopy will remain largely unchanged by NOTES.

The Future of NOTES

While it is improbable that we are on the brink of widespread pure clinical NOTES, there are many potential applications of NOTES that will likely manifest. Given the portability of NOTES equipment and the requirement for only conscious sedation, natural orifice surgery is ideally suited for the intensive care unit. There are two potential scenarios that have been described that are amenable to ICU NOTES: diaphragm pacing and peritoneoscopic examination for ischemic bowel.

Diaphragm pacing has been shown to be effective in promoting ventilator weaning in a wide variety of clinical situations.[38] The procedure is commonly performed laparoscopically in the operating room with insertion of pacing wires into both hemidiaphragms and externalization of the wires. The procedure of insertion could be performed through a gastrotomy. Performing a NOTES placement of diaphragm pacing wires in the ICU might obviate the need to transport a critically ill patient to the operating room.

Another ICU scenario amenable to NOTES is the question of necrotic small bowel in cases of potential mesenteric ischemia.[39] These types of patients are usually critically ill and cannot tolerate a trip to the comuted tomography (CT) scanner. The presence of ischemic small bowel might be confirmed with transgastric peritoneoscopy. Should a short segment of ischemic small bowel be visualized, the patient could be triaged to the operating room. Extensive small bowel necrosis might not be suitable for an operation, and the costs associated with a nontherapeutic laparotomy would be spared.

The minimal equipment requirements and the need for high-level disinfection, rather than sterilization, make NOTES appropriate for developing regions of the world. NOTES could be performed without the infrastructure requirements of an operating room and sterilization equipment. The light source, video processor, and monitor could be easily transported from region to region to best serve populations in need. NOTES might be the means to bring surgical care to underserved peoples.

The transportable nature of NOTES might be applicable for battlefield abdominal exploration. A far-forward facility could be arranged to explore the abdomen after serious blunt trauma. Hemostasis might be achieved with topical hemostatics or endoscopically placed packing. Once stabilized, the patient could then be transported to a higher echelon of care for definitive management.

Even if pure NOTES does not reach clinical fruition, there are many offshoots from NOTES technology that will likely be applicable to gastrointestinal surgery and endoscopy. The need for improved endoscopic instrumentation has been identified through NOTES research. Endoscopic scissors, graspers, and sewing devices developed for

NOTES might be useful in performing endoscopic mucosal resections or even full-thickness resections and closure of inadvertent perforations.

Another possible derivative of NOTES is single port laparoscopy. As an example, a cholecystectomy might be performed through a single 10-mm umbilical port. A flexible laparoscope could be maneuvered into position and locked into place. Novel triangulating instruments with multiple degrees of freedom could then be used for the dissection. Specimen removal would then occur through the single umbilical port.

Critiques

It is tempting to be swept up in the enthusiasm for NOTES, but hard data supporting the clinical applications of NOTES need to be accumulated before widespread enactment. NOSCAR posed the germane questions regarding the safety and utility of NOTES in the White Paper, and some of the answers are manifesting.

The infectious implications of transvisceral surgery may not be as detrimental as originally presumed. Certainly, bacteria will gain access to the abdominal cavity, but the peritoneum may be efficient at clearing the microbes. After all, the bariatric surgeon is not overly concerned about the gastrotomy contaminating the peritoneal cavity during construction of the proximal anastomosis. Whereas a temporary open gastrotomy is likely not harmful, peritoneal soilage from a leaking closure may be devastating. Therefore, a substantial amount of effort should be devoted to assuring a reliable method of viscerotomy closure.

Other laboratory work substantiates optimism regarding NOTES. Evidence is accumulating that the immune impact of NOTES is equivalent to laparoscopy. Some groups are developing ingenious methods of intraabdominal retraction and dissection. Novel methods of transgastric access might simplify the issue of reliable closure. In aggregrate, these data might be a further evidence that there is a role for NOTES in gastrointestinal surgery.

However, an overly sanguine view of NOTES is unrealistic. Besides the prototypes used in the laboratory, most currently available equipment is inadequate for performing retraction, meticulous dissection, and bimanual manipulations. Importantly, there is no reliable, simple, and safe method for achieving full-thickness, water-tight closure of the viscerotomy. NOTES will remain constrained until better instruments are developed.

Many consider NOTES a technology without an application. At present, this is generally true. Routine NOTES cholecystectomies or appendectomies (i.e., those not under the aegis of an approved clinical trial) should probably not be performed until laboratory and technical advances materialize. Contrarily, there are likely a limited number of applications that are well-suited to the current iteration of NOTES. PEG rescue is a simple procedure that relies on available equipment and could have a role in patients with early dislodgement of a PEG tube.

NOTES does not signal the demise of traditional gastrointestinal surgery or laparoscopy. It is plainly evident that extraordinary advances are required before NOTES can be considered for widespread application. Rather than succumbing to the fervor for NOTES, we must take a circumspect view of NOTES. Diligent laboratory research is imperative, followed by cogent clinical trials.

Above all, regard for patient safety must prevail. Only those with vast laboratory experience with NOTES should contemplate clinical NOTES procedures. Initially, only patients enrolled in clinical trials should undergo NOTES. Finally, the burden is on NOTES investigators to perform due diligence on this nascent field and ensure that we are doing the right thing for our patients.

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