

26. Natural Orifice Transluminal Endoscopic Surgery (NOTES™)

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Introduction

Natural orifice transluminal endoscopic surgery (NOTES) refers to the performance of surgical procedures using transvisceral access to the body cavities. By eliminating body wall incisions, NOTES offers the potential for less postoperative pain, improved cosmesis, and faster functional recovery.

Less than a decade after the first report of a NOTES procedure in an animal model, an explosion of research has led to the development of several novel procedures. This work has left the lab and is already being translated to the bedside. Thousands of NOTES procedures have been performed across the globe. Peroral endoscopic myotomy (POEM) is a procedure not even imagined 10 years ago already threatening to replace traditional Heller myotomy as first line therapy for achalasia. Moreover, the interest spurred by NOTES has had major “trickle-down” effects, with spillover benefits for interventional flexible endoscopic and laparoscopic surgery.

This chapter will review the history of NOTES, the role of SAGES/ASGE (The Society of American Gastrointestinal Surgeons/American Society of Gastrointestinal Endoscopy) in fostering NOTES, a brief update on the current status of various NOTES procedures, and highlight remaining challenges for the future.

History

The first pure NOTES procedure—a transgastric peritoneoscopy in a porcine model—was published in 2004 [1]. Subsequently, a video case report of a human transgastric appendectomy was presented at the 2005 SAGES meeting [2]. These reports spurred an explosion of laboratory work that demonstrated multiple other NOTES procedures could be safely performed in animal models [3–5].

In October 2005, a joint meeting sponsored by SAGES and ASGE was held in New York City. This meeting spawned the Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR). NOSCAR was founded to facilitate research and communication among investigators, thereby promoting the safe development of NOTES procedures for clinical practice.

One outcome of the initial October 2005 meeting was the drafting of the first White Paper on NOTES [6]. This paper defined the initial barriers to NOTES—including safe access to the peritoneum, gastric closure, prevention of peritoneal infection, development of a multitasking platform, and the management of complications related to peritoneal insufflation. The group also identified several key research questions to be answered to overcome these barriers.

Five years later, the 2nd SAGES/ASGE NOTES white paper was published and summarized the progress made in surmounting the originally identified challenges [7]. All the key research questions had been tackled—most with NOSCAR sponsorship. Of the initially identified barriers, several had been answered completely (e.g., peritoneal infection, physiologic complications) while significant technologic progress had been made to address the others (Table 26.1).

Clinical Trials

Transvaginal NOTES vs. laparoscopic cholecystectomy

Transanal NOTES hybrid sigmoid colectomy

Transvaginal NOTES sleeve gastrectomy

Transvaginal ventral hernia repair

Transrectal NOTES appendectomy

Table 26.1. Progress on seminal questions of first NOTES white paper.

Question	Progress
Peritoneal access	All access points in human clinical practice
Gastric closure	New devices for closure developed, testing in animal models
Prevention of infection	Minimal peritoneal contamination demonstrated after transgastric access
Suturing and anastomotic devices	New devices approved or in pipeline
Maintaining spatial orientation	Image registration and other techniques being explored
Development of a multitasking platform	Device prototypes in development
Management of intra-peritoneal complications and hemorrhage	Currently through laparoscopic rescue in hybrid approaches. Better instrumentation still required
Physiologic untoward events caused by NOTES	Risks, physiology, and treatment documented in animal and humans
Training	Advanced flexible endoscopic fellowships

Amazingly, in only 5 years, over six human clinical trials of NOTES procedures were underway in the US alone, some for procedures not envisioned at the first NOSCART meeting.

The pace of innovation with NOTES procedures was rapid during the early years, but the current economic and regulatory environment have slowed the rate of innovation in the past several years (Fig. 26.1).

Current Status of Procedures

The procedures and operations that have been attempted with a NOTES approach are too exhaustive to document here. Suffice to say that nearly every conceivable abdominal, pelvic, and thoracic operation has been attempted with a NOTES approach in animal models. Below we will focus on the most common or promising NOTES operations in development today, grouped by visceral access point (Table 26.2).

Transesophageal

The best example of transesophageal access is peroral endoscopic myotomy (POEM) (Fig. 26.2). POEM was first described in 2007 in an animal model [8]. Subsequently, POEM has become the most clinically

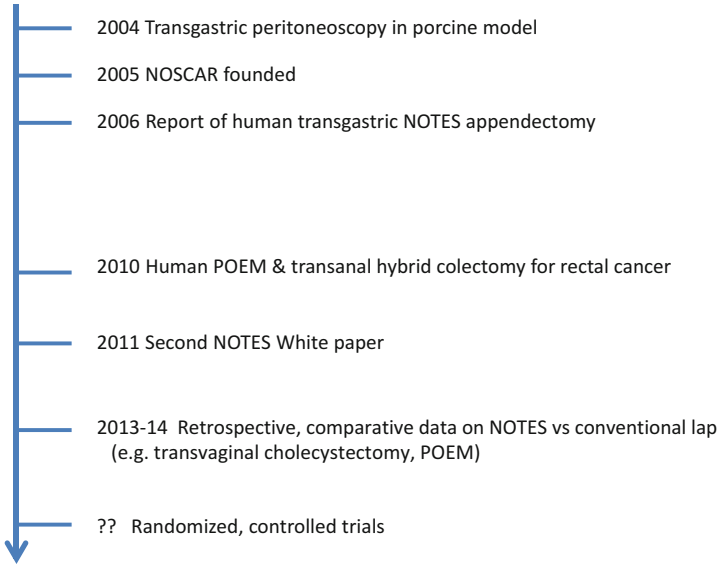


Fig. 26.1. Timeline of NOTES progress.

Table 26.2. Prototype NOTES procedures grouped by visceral access site.

Visceral access	Prototype procedure
Esophagus	Heller myotomy (POEM)
Stomach	Diagnostic peritoneoscopy
Vagina	Cholecystectomy
Rectum	Proctocolectomy

successful NOTES procedure, driven initially by Dr. Haru Inoue in Japan [9].

The technical details of POEM are reviewed elsewhere in this book. It is now clear that POEM is safe in experienced hands and, at least in the medium term, an effective treatment for achalasia. There had been initial concern that the lack of an accompanying anti-reflux procedure with POEM might lead to increased rates of GERD and, potentially, recurrent dysphagia. Thus far, retrospective, non-controlled studies have not observed high rates of symptomatic reflux [10]. Long term and

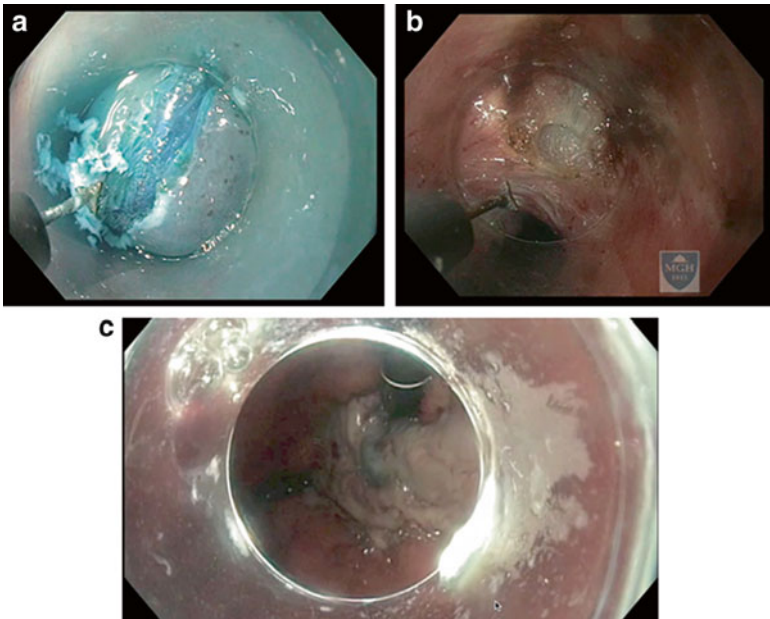


Fig. 26.2. Per oral endoscopic myotomy. (a) Creation of the esophageal mucotomy. (b) Division of circular esophageal muscle fibers within submucosal tunnel. (c) Retroflexed view within stomach showing the completed myotomy extending past the GE junction.

randomized, controlled studies comparing POEM and laparoscopic Heller myotomy are still needed.

Transesophageal access has also been explored for mediastinal and thoracic procedures. Using a submucosal flap tunnel method, like POEM, transesophageal NOTES has been used for mediastinal lymph node biopsy and lymphadenectomy, pericardial windows, and pleural biopsy in animal models [11]. One of the limitations of transesophageal access is the consequences of an esophageal leak. Although these can frequently be managed nonsurgically, the morbidity of mediastinitis is significant. Another limitation of transesophageal access is the restricted flexibility imposed by the narrow intramural esophageal tunnel used to transgress the esophageal wall. Finally, since the esophagus cannot be fully sterilized, it is not a good route for placing foreign bodies or implants.

Transgastric

The first NOTES procedures used transgastric access to the peritoneal cavity. Diagnostic peritoneoscopy, appendectomy, cholecystectomy, oophorectomy, and more complex procedures such as splenectomy have all been successfully performed via transgastric access in animal models.

Many of the initial barriers delineated in the 1st SAGES white paper dealt with transgastric access. These barriers continue to limit full use of transgastric NOTES. Formation of the gastrotomy has been complicated by high rates of iatrogenic injury to the abdominal wall, viscera, or vessels [12]. Performance of procedures in the upper abdomen requires a retroflexion of the gastroscope which limits mobility, and hence, this access route can add technical challenges not present in laparoscopy. Thus far, human transgastric NOTES has been limited to less technically complex procedures where the endoscope can be used in an in-line, or straight, position such as appendectomy or peritoneoscopy.

Significant progress towards improving gastrotomy closure has been made, with several new devices being tested. Importantly, animal studies have shown that peritoneal contamination is not likely to be clinically significant from transgastric access—akin to a clean-contaminated open or laparoscopic case [13, 14]. However, given that transgastric NOTES is being pursued to replace clean operations, the reliability of visceral closure will need to be extremely high to allow routine clinical practice. Nevertheless, transgastric staging peritoneoscopy remains an enticing approach for evaluating malignancies that require biliary stenting or other endoscopic interventions in preparation for aggressive local therapies such as surgery or radiotherapy. The procedure was among the top candidates listed for initial human application at the 2010 NOSCAR meeting, given its wide potential application and benefit, as well as the availability of appropriate instrumentation [7].

Transvaginal

Transvaginal access has gained significant traction due to its advantages of an in-line endoscopic view for abdominal operations and a reliable and safe visceral closure method derived from long experience in the gynecologic field. Indeed, one of the first NOTES-types procedures was a hybrid transvaginal cholecystectomy performed during vaginal hysterectomy incorporating transvaginal and abdominal ports [15].

Transvaginal cholecystectomy has become the most common clinical hybrid NOTES procedure. It is estimated over 4000 have been performed worldwide [3]. A large experience has been reported in Europe through the German registry [16]. In many parts of the world, transvaginal cholecystectomy is considered a fairly standard approach. To date, primarily due to instrument limitations, transvaginal cholecystectomy is still a hybrid NOTES procedure, with abdominal ports used for securing the bile duct and vascular supply.

Dissemination of this technique is hindered by its applicability only to women, as well as residual functional and cultural concerns over transvaginal access. Injuries to the ureter, bladder, and rectum have been reported, although in most studies, the overall complication rate with NOTES transvaginal cholecystectomy is equivalent to laparoscopic cholecystectomy. Some critics have raised concerns about the impact of transvaginal access on sexual and reproductive function. Several studies addressing this topic in transvaginal cholecystectomy have not borne these concerns out, and there is fairly extensive data in the gynecologic literature that should also allay concerns [17, 18].

A small randomized trial of transvaginal vs. multi-trocar needle-scope cholecystectomy showed decreased pain scores and improved cosmesis with the NOTES approach. There was no observed difference in return to work or complications, although the study was underpowered [19]. A larger multi-institution clinical trial comparing NOTES transvaginal cholecystectomy with laparoscopic cholecystectomy sponsored by NOSCAR is underway.

Transanal

Transanal access, particularly for colorectal resection, offers many potential advantages. Most importantly, the access viscerotomy is through the target organ and is removed at the time of resection. Multiple tested and reliable means of closure are available, included stapled anastomosis or hand-sewn coloanal anastomosis. With the transanal endoscopic microsurgery (TEM) experience, a multitasking instrumentation platform is available and familiar to many surgeons. Lastly, transanal access provides immediate access to the correct tissue planes for dissection, allowing potentially improved visualization for a “bottom-up” dissection in the pre-sacral space for low rectal resections (Fig. 26.3) [20].

The first hybrid NOTES transanal rectal resection with laparoscopic assistance was reported in 2010 [21]. Since that time, several series of

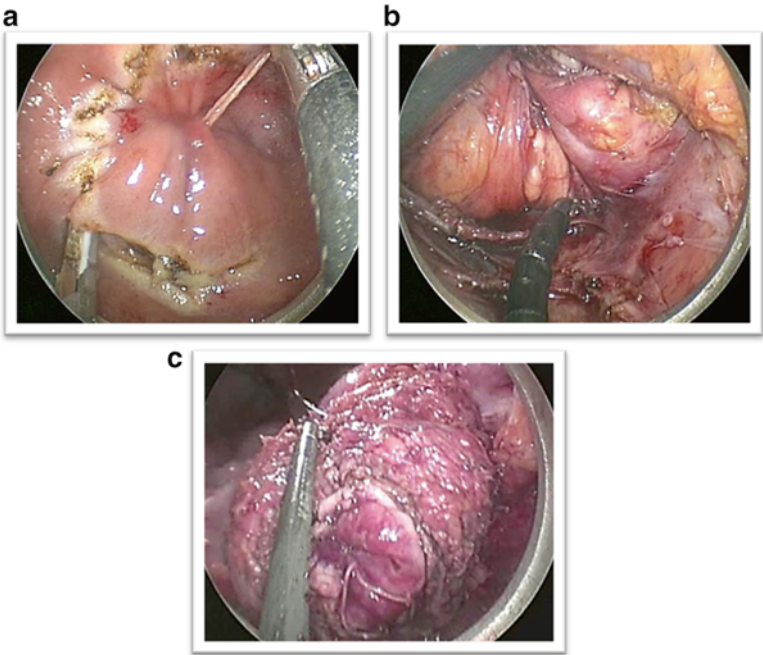


Fig. 26.3. Transanal NOTES colectomy. (a) Transrectal access by full thickness circumferential rectal division using the ultrasonic dissector. The purse string suture marks the distal resection margin. (b) “Bottom-up” NOTES dissection of the pre-sacral space. (c) Transanal extraction of rectal resection specimen.

hybrid NOTES colorectal resection for rectal cancer have been reported, and it is estimated >400 human procedures have been performed worldwide [20, 22]. These series have demonstrated feasibility and safety. Importantly, they have demonstrated excellent oncologic outcomes, with good lymph node harvest and negative pathologic margins.

Due to current limitations with instrumentation, laparoscopic assistance is still required for splenic flexure takedown and vascular pedicle ligation. However, transanal sigmoid resection offers considerable promise for benefits: the transanal view allows precise identification of the distal tumor resection margin, improved visualization for dissection in obese patients and the narrow pelvis, and NOTES specimen extraction eliminates the problems associated with a larger abdominal incision, including increased pain, wound infections, and hernia. Future trials will need to confirm whether these benefits are realized and importantly, assess long-term oncologic outcomes.

Ongoing Challenges

As discussed, considerable progress has been made towards overcoming the challenges associated with NOTES. In particular, concerns over physiologic and infectious complications of transvisceral access to the peritoneum have largely been addressed. Several of the other obstacles noted in the 1st NOTES white paper have been lowered but remain.

Future Challenges

- Transgastric access and closure
- Regulatory hurdles to device development
- Reimbursement and cost incentives
- Improved instrumentation and platform to go from hybrid to pure NOTES
- Training paradigm
- Randomized data to assess outcomes

Technical challenges related to placement and closure of viscerotomy—particularly for transgastric access—still exist. Devices for gastrotomy closure have improved and been tested with some reliability including over the scope clips. It is likely feasible to safely achieve natural orifice access with laparoscopic assistance to guide placement of the viscerotomy and to test closure. However, a reliable method for safely creating and orienting the viscerotomy, particularly in the stomach, using a pure NOTES approach is lacking. Similarly, a pure NOTES or endoscopic method to test the integrity visceral closure intra-procedurally has not yet been described.

Technical problems related to instrumentation deficiencies that would allow pure NOTES procedures are currently being overcome by use of hybrid laparoscopic assisted procedures. In particular, current instrumentation for hemostasis—clip applicators, vessel sealing, and other energy devices—remain inferior on flexible NOTES platforms. Endoscopic stapling and anastomotic devices have been introduced but remain suboptimal. The ongoing development of endoscopic suturing devices, however, has been more successful with commercially available devices now on the market.

Likely the greatest challenge to NOTES is the current regulatory and financial environment, which could slow development of needed new devices and technology. Previously, devices could be more quickly approved using the FDA 510K process. Physicians were allowed to use approved devices for “off-label” indications. Increasing scrutiny is being applied to this process, and more devices are being required to undergo the more arduous, costly, and time-consuming pre-marketing approval application (PMA). As many of the companies focusing on NOTES device development are smaller start-ups with smaller budgets, these regulatory changes are major challenges to further innovation.

Finally, with the recent changes of healthcare reform, greater attention will be paid going forward to the costs of new procedures. It must be understood that the initial costs of a new, innovative procedure will be greater at its outset than in its final form. We must not lose sight of the potential longer term benefits of a new procedure, particularly in societal costs that are often not captured with current studies (e.g., disability, return to work, long-term complication and re-op rates). In the early days of laparoscopic cholecystectomy, costs were higher than open surgery, but over time, the cost-benefit ratio has clearly swung in favor of laparoscopy. Developing a viable financial strategy to nurture innovative procedures through their more costly infancy must be a priority for hospital and medical leaders.

Future Directions

NOTES currently stands at an exciting transitional phase. Many of the initial physiologic concerns and technical limitations have been addressed or have promising solutions in the pipeline. Many NOTES procedures have graduated from the lab and been successfully introduced into human practice. Going forward, our goal must be to continue clinical translation, optimize technique and costs, and rigorously assess NOTES procedures for safety and comparative efficacy.

The “trickle down” benefits associated with NOTES have been significant. Many instruments and devices developed with NOTES in mind have found uses in interventional endoscopy and single site laparoscopic surgery. Cross-fertilization between these fields, particularly in training and development of technical skills, will be critical to the future of endoscopic surgery. Of interest is the potential application of robotics for single port and endoscopic surgery. Articulated, flexible robotic instrumentation could aid in overcoming some of the triangulation and

visualization challenges associated with current single-site laparoscopic platforms. The cost of the current computer assisted surgery systems is prohibitive, but if these costs come down there may be potential applicability for this technology in NOTES. Improvements in instrumentation will be necessary to drive the transition from hybrid to pure NOTES procedures.

The 2nd NOTES white paper noted debate on the ideal entry procedure for NOTES. Since that time, POEM has clearly succeeded as the first pure NOTES operation in widespread practice. Transanal NOTES colectomy remains technically challenging but has many conceptual advantages supporting its candidacy as the second NOTES procedure to enter wider clinical practice. It is critical that clinical entry continue in the hands of experienced teams with prospective documentation of outcomes.

The past decade has seen development of NOTES procedures that are safe and effective. The next major hurdle is to put NOTES to the test in randomized clinical trials against standard laparoscopy. The time is nearing to see whether NOTES will offer the originally envisioned patient benefits of reduced pain, improved cosmesis, and faster functional recovery.

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