Recent advances in natural orifice transluminal endoscopic surgery†

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Summary

Natural orifice transluminal endoscopic surgery (NOTES) has emerged as one of the most exciting areas in the field of minimally invasive surgery during the last decade. NOTES comprises a wide spectrum of procedures from various natural accesses such as transgastric or transvaginal routes, and different direct-target or distant-target organs. Since polypectomy was first performed in 1955, major advances in technology and refinement of endoscopic technique have allowed endoscopic surgeons to perform complex endoscopic interventions such as endoscopic submucosal dissection. Recognizing the safety and feasibility of submucosal tunnelling and mucosal closure, endoscopic resection beyond the level of mucosa has been increasingly reported. One of these procedures, peroral endoscopic myotomy for achalasia, has gained much popularity and excellent results have been published comparable with that of traditional Heller cardiomycotomy. Submucosal tunnelling endoscopic resection has also been reported for tumors situated in the muscular layer of the gastrointestinal tract. To overcome the difficulty of intestinal closure after NOTES, researchers have collaborated with the industry in developing different endoscopic suturing devices such as the Eagle Claw (Olympus Medical Systems, Tokyo, Japan) and Overstitch™ (Apollo Endosurgery, Austin, TX, USA). These devices allow precise and secure suture application with the ordinary flexible endoscope, achieving tissue approximation similar to open surgical suturing. To further expand the potential of NOTES, investigators had also developed multitasking platforms enabling the performance of surgical procedures of even higher complexity. Recently, a novel endoscopic robotic system ‘Master and Slave Transluminal Endoscopic Robot’ (MASTER) has been developed. Early results of endoscopic resection utilizing this system have been encouraging, allowing both experts and novices in endoscopy to perform difficult endoscopic resection with a high degree of flexibility.

Keywords: Minimally Invasive Surgery • Endoscopy • Oesophagus

HISTORY OF NATURAL ORIFICE TRANSLUMINAL ENDOSCOPIC SURGERY

The history of endoscopic surgery began in the 1950s, when the first polypectomy was performed in the colon with a rigid endoscope [1]. In 1973, Deyhle reported a successful snare polypectomy on a sessile colonic polyp after saline submucosal injection [2]. Since then, tremendous advance has been made in the technology of endoscopy allowing the development of different methods in endoscopic resection. Ono et al. [3] reported the first endoscopic submucosal dissection (ESD) for the treatment of early gastric cancer in 2001. This technique involved submucosal injection of a mixture of dye, saline and adrenaline followed by circumferential dissection of target lesions with specially designed electrosurgical knives to achieve the wide margin resection of early gastric cancers. The procedure had since gained widespread popularity in treating early neoplasia of both the upper and lower gastrointestinal tract. When compared with endoscopic mucosal resection, ESD has been shown to improve en bloc resection and histological complete resection rate for early mucosal gastric cancers [4, 5]. In 2004, Kalloo et al. [6] reported the first transgastric peritoneoscopy in a porcine model. Rao and Reddy presented the video of the first human transgastric endoscopic appendicectomy at the 2004 Annual Conference of the Society of Gastrointestinal Endoscopy of India. The term natural orifice transluminal endoscopic surgery (NOTES) was coined for these novel procedures soon afterwards. In October 2005, the NOTES white paper was released which stated a number of issues that had to be overcome before the procedures could be fully implemented in human subjects [7]. Since then, there was an exponential growth in publications relating to NOTES, both in animal and in human studies. Jacques Marescaux reported the first human transgastric cholecystectomy in 2007 [8]. Up till now, more than 1900 NOTES cholecystectomies via transvaginal or transgastric route had been reported [9–18]. However, NOTES has not gained worldwide application as laparoscopy did in the first decade after its introduction. This is mainly due to the high technical demand for most of these procedures where only few surgeons could master. Nonetheless, the innovation in different NOTES procedures

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has led to the development of technology that could be incorporated into daily clinical practice.

CLASSIFICATION OF NOTES

Atallah et al. [19] proposed a subdivision system for all procedures coined NOTES (Table 1). Direct-target NOTES operations do not violate a healthy visceral organ to gain access to another, whereas a distant-target NOTES operation approached a distant organ through luminal entrance of another organ [19]. Examples of distant-target NOTES include transvaginal cholecystectomy and transgastric appendicectomy. These procedures were more commonly reported by researchers from western countries. On the other hand, the development of direct-target organ NOTES techniques has been more popular in Asia. Examples include peroral endoscopic myotomy (POEM) and peroral endoscopic tumour resection.

Transanal NOTES is a fusion of four different surgical approaches including transanal endoscopic microsurgery [20]/transanal minimally invasive surgery [21], transanal–transabdominal operation (TATA) [22], total mesorectal excision (TME) [23] and NOTES [19]. The development of TATA was the prequel to transanal TME, being proposed for low-lying distal rectal tumours aimed at achieving adequate distal resection margin while increasing the likelihood of sphincter preservation [23]. Transanal TME is typically performed as a hybrid procedure, although pure NOTES transanal TME procedures have also been reported in recent 2 years [24, 25]. Latest modifications in the technique of transanal TME include adaptation of the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, California, USA) for robotic transanal TME [26, 27].

On the other hand, the application of NOTES in thoracic surgery has only been scarcely reported and mostly limited in animal studies [28–38]. Transtracheal or transoesophageal access to the mediastinal and pleural cavity had both been described. The slow development and application of thoracic NOTES could be attributed to the close proximity of major vital structures, the devastating results of mediastinitis and the lack of familiarity of cardiothoracic surgeons with flexible endoscopy [39]. Nonetheless, innovative surgical approaches, such as transumbilical thoracic sympathectomy, have been successfully performed with satisfactory clinical outcomes [40, 41]. Electromagnetic navigational bronchoscopy is another emerging technology that could help surgeons to sample outcomes [40, 41]. Electromagnetic navigational bronchoscopy is another emerging technology that could help surgeons to sample another emerging technology that could help surgeons to sample

and treat small peripheral lung lesions via an endoscopic approach [42, 43]. By combining virtual and conventional bronchoscopy, these small or peripheral lung lesions could be accessed safely for biopsy and even therapeutic strategies such as microwave and radiofrequency ablation.

SUBMUCOSAL TUNNELLING TECHNIQUE AND ITS APPLICATION

Table 2 summarizes the key barriers of NOTES identified in the 2005 first white paper from the American Society of Gastrointestinal Endoscopy (ASGE)/Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) working group [7]. Safe and optimal peritoneal access was the first major barrier to overcome. While transvaginal route has been extensively investigated owing to the ease of secure vaginal closure, transgastric route remained an appealing approach because it is more universal and often more appealing to patients [44]. However, safe transgastric peritoneal access is more difficult than the transvaginal route. In 2007, Sumiyama et al. [45] reported the use of submucosal endoscopy with mucosal flap safety valve in pigs, now commonly named as submucosal tunnelling technique. High-pressure carbon dioxide submucosal injection and balloon dissection were utilized to create a large submucosal working space for the insertion of a cap-fitted endoscope. Peritoneal cavity could be accessed afterwards by the incision through the muscularis propria of the stomach (or intestine), and secure closure of the defect achieved with simple clipping of the mucosal entry site (Fig. 1).

POEM, first performed in humans by Prof H. Inoue in 2008 to treat achalasia, is one of the major clinical applications of the submucosal tunnelling techniques in NOTES [46]. The procedure involved a long submucosal tunnel created in the oesophagus (mean: 12.4 cm), followed by myotomy of the lower oesophageal sphincter identical to a surgical cardiomyotomy. The mucosal defect was finally closed with endoscopic clips. Initial case series of POEM reported encouraging results. There was a significant reduction in the dysphagia score after POEM as well as an improved lower oesophageal sphincter pressure on oesophageal manometry studies [47–49]. A recent meta-analysis of 1045 POEM procedures verified these findings upon pooled analysis. Five cohort studies compared the results of POEM (n = 90) with laparoscopic Heller’s cardiomyotomy (n = 160), which showed comparative efficacy, postoperative analgesic requirement, adverse events and development of post-procedure GER, in the treatment of achalasia [51–55]. Randomized trials are currently underway.

Table 1: Subdivisions of NOTES

<table>
<thead>
<tr>
<th>Division</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Type of operation performed</td>
<td>Cholecystectomy, appendicectomy</td>
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<tr>
<td>Orifice used</td>
<td>Transoral, transvaginal, transanal</td>
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<tr>
<td>Distant-target versus direct-target organ</td>
<td>Transanal TME (direct); transgastric appendicectomy (distant)</td>
</tr>
<tr>
<td>Pure versus hybrid versus pure combined orifice</td>
<td>Laparoscopic-assisted transanal TME (hybrid); transvaginal appendicectomy (pure); transvaginal and transgastric nephrectomy (pure and combined)</td>
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<td>Flexible versus rigid instruments</td>
<td>Transgastric appendicectomy (flexible gastroscopes); transanal TME (Rigid; using TME or TAMIS)</td>
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NOTES: natural orifice transluminal endoscopic surgery; TME: total mesorectal excision; TAMIS: transanal minimally invasive surgery.

Table 2: Potential barriers of NOTES

**Potential barriers to clinical practice**

1. Access to peritoneal cavity
2. Gastric (intestinal) closure
3. Prevention of infection
4. Development of suturing and anastomotic devices
5. Spatial orientation
6. Development of a multitasking platform to accomplish procedures
7. Management of intra-peritoneal complications
8. Physiological untoward events
9. Compression syndrome
10. Training
11. Other

NOTES: natural orifice transluminal endoscopic surgery.
A submucosal tunnelling technique was also utilized to resect gastrointestinal tumour arising from the deep submucosal or muscular layer. Lee et al. [56] reported the first case of submucosal tunnelling resection of a gastric subepithelial tumour under conscious sedation. Multiple case series were reported subsequently, the largest one consisting of 85 cases [57–61]. Most tumours were benign tumours arising from the oesophagus and cardia. The technical success rate was 100%, achieving complete resection in all cases. There is so far no report on the occurrence of major complication [60]. However, this resection technique is limited by the maximal size of tumour that could be retrieved via the oral route, usually around 4 cm. There would also be minimal resection margin and thus controversies abound on resection of submucosal tumours of high malignant potential.

**CLOSURE OF INTESTINAL DEFECT: DEVICE DEVELOPMENT**

Another important barrier identified in the NOTES white paper was closure of the resultant intestinal defect. The ability to achieve secure luminal closure is pivotal to the success of NOTES. Throughout the years, researchers have collaborated with the industry in the development of devices that would facilitate closure of these defects, including various clipping and suturing systems.

Endoclips were considered not secure enough given the low bursting pressure after closure in ex vivo studies [62,63]. ‘Over-the-scope-clips’ (OTSC; Ovesco Endoscopy, Tübingen, Germany), on the other hand, allow approximation of tissue similar to a surgical clamp [64]. Comparable leak pressures could be achieved with the use of OTSC compared with hand-sewn closure in animal studies [65–67].

Eagle Claw (Olympus Medical Systems, Tokyo, Japan), initially designed by our group to perform endoscopic plication of bleeding peptic ulcer [68,69], was subsequently investigated for suture closure of intestinal defect after NOTES (Fig. 2). It consisted of opposing jaws with a detachable needle to which a 3-0 nylon stitch is mounted. After stitching each side of the gastric defect, closure was complete on tightening of the suture by a metal pusher. In the survival experiment on porcine models, 10 gastrostomies were successfully closed and none of the animals suffered from suture line leakages upon post-mortem after 2 weeks [70]. Overstitch™ (Apollo Endosurgery, Austin, TX, USA), another endoscopic tip-mounted suture device now commercially available, has also been proved to provide secure closure of gastric defect in animal survival study [71].

**DEVELOPMENT OF MULTITASKING PLATFORMS**

The conventional endoscopes were originally designed solely for diagnostic purpose and thus did not possess the quality to achieve fine tissue handling as in open or laparoscopic surgery. The key to success in NOTES would therefore be a multitasking endoscopic-based platform that would enable the performance of complex surgical manoeuvres such as dissection and suturing. These systems should provide a flexible, yet stable platform where NOTES procedures can be performed universally through any of the transluminal approaches. A stable image of the operating field, independent of the movements of the working arms, is essential, as well as ergonomic user interfaces to control the movements of the arms [72]. Examples of these systems developed by different manufacturers include EndoSAMURAI® (Olympus Medical Systems), ANUBIScope™ (Karl-Storz, Tuttlingen, Germany), TransPort™ Multi-lumen Operating Platform (USGI Medical, California, USA) and Direct Drive Endoscopic System (DDES; Boston Scientific, Massachusetts, USA). Superior performance time and accuracy were achieved with both the EndoSAMURAI and DDES systems compared with a dual-channel endoscope in a bench-top simulation setting [73–75]. However, human studies on these multitasking systems are currently lacking.

A novel endoscopic robotic system, the Master and Slave Transluminal Endoscopic Robot (MASTER), was reported by Sun et al. [76] (Fig. 3). It consisted of a master console, a tele-surgical workstation, and a slave robotic manipulator that holds two end-effectors: a grasper and a monopolar electrocautery hook. In a multicentre study, robotic ESD was successfully performed in 5 patients with early gastric neoplasia utilizing the MASTER system [77]. Median time for submucosal dissection was 18 min (3–50 min) and no patient encountered any post-procedural complication. Last year at Digestive Disease Week 2014, we reported an ex vivo animal study using this MASTER system [78]. Nine participants, including three non-endoscopist novices, were instructed to perform ESD in porcine stomach models. All of them were able to complete the procedures without any perforation of the stomach. A trend towards superior performance among experts in ESD when using the MASTER system was observed. Yang and colleagues [79] developed another novel flexible ‘snake'
robot for endoscopic surgery and a bench-top study was recently reported by the group, demonstrating significantly greater accuracy of targeting at a retroflexed position compared with a conventional endoscope.

DEVELOPMENT OF NOTES IN ASIA

Over the past 10 years, different groups have been formed to enhance collaboration and report on outcomes in NOTES. The Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR) was founded in 2005, a joined group from the SAGES and the ASGE. Two white paper summaries have been published in 2006 and 2011, with the aim to assess the potentials of NOTES, to facilitate research on NOTES, to insure the protection of patients during implementation of NOTES and to report on current development in this evolving and dynamic field. In 2006, the Asia-Pacific Working Group in NOTES was established in Asia. Since then, experienced endoscopists and laparoscopic surgeons from Hong Kong, China, Singapore, India, Malaysia, Korea and Japan have gathered every year and this working group has created a platform for sharing the experience and discussion of NOTES future development among different countries in Asia.

CONCLUSION

NOTES represents a major conceptual and technological advance in the field of surgery and endoscopy since the advent of laparoscopy. It has yet to be widely adopted into daily clinical practice owing to technical challenges. However, innovation from researchers had led to the development of some groundbreaking procedures like POEM, which truly represents a 'scarless' surgery. It can be anticipated that with further advances in both technology and experience, the concept of NOTES would be realized in achieving even more complex surgical procedures through a stable multitasking surgical platform with good image quality and highly flexible, precise instruments.

Conflict of interest: none declared.

REFERENCES


