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The dawn of "New NOTES": a review

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Abstract

The central idea behind the aim to implement traditional NOTES into clinical practice was to provide a scarless and safer surgery for the patient. Despite the failure of traditional NOTES in the purest sense, years of research that looked into developing a safe access into the peritoneum for NOTES have not been wasted but instead, have paved the way for the growth of the New NOTES. A decade after the advent of traditional NOTES, New NOTES procedures such as per oral endoscopic myotomy (POEM), per oral pyloromyotomy (POP), endoscopic full-thickness resection (EFTR) and submucosal tunneling endoscopic resection (STER) have flourished with increasing worldwide adoption. Submucosal dissection and tunneling, being the basis of all New NOTES procedures, serve as an initial necessary skill for future New NOTES operators. We will briefly review the major applications of the new NOTES procedures.

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Key Words: New NOTES, per oral endoscopic myotomy, per oral pyloromyotomy, endoscopic full-thickness resection, submucosal tunneling endoscopic resection.

INTRODUCTION

Natural orifice transluminal endoscopic surgery (NOTES) is arguably the most important innovation in the field of surgery since Phillipe Mouret of France performed the first laparoscopic cholecystectomy in 1987[1]. NOTES was an exciting ground-breaking technique, not only for endoscopists and surgeons but also for patients, as it envisioned a scarless intervention with a shortened post-operative recovery time, without the daunting issues of incisional hernias and surgical site infections[2]. After more than a decade since its introduction by Kalloo and Kantsevoy[3], traditional NOTES has not been successfully implemented worldwide owing to many unanticipated obstacles such as gastric closure, suturing, anastomotic devices and triangulation of instruments[4]. With dedicated and intensive research in the field of traditional NOTES, a novel field of endoscopy emerged and the term 'New NOTES' was coined. The procedures included in New NOTES are, namely, per oral endoscopic myotomy (POEM), Per-oral pyloromyotomy (POP), endoscopic full thickness resection (EFTR) and submucosal tunneling endoscopic resection (STER). Since the playing field for New NOTES is based on third-space, operators should possess advanced skills in endoscopic submucosal tunneling (ESD) technique[5]. Our main goal in this review is to describe the current applications of the New NOTES techniques.

1. NOTES: a historical timeline

To properly grasp the development of the New NOTES, one has to appreciate the progression of traditional NOTES[6]. The concept of Natural Orifice surgery was first conceived by Sergey

Kantsevoy and Tony Kalloo in the 1990s. In 1997, along with other physicians, Sydney Chung, Peter Cotton, Chris Gostout, Rob Hawes, and Jay Pasricha came together to form the Apollo group with one goal in mind: to innovate the application of therapeutic NOTES[6]. In July 2005, 12 pioneers were selected by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) and the American Society for Gastrointestinal Endoscopy (ASGE) to form the Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR)[7]. The main goal of NOSCAR was to assess the safety, efficiency, indications and ethical aspects of NOTES[7]. Subsequently, 5 years after its implementation, NOSCAR published a 5-year progress report on NOTES, which outlined the progress and limitation of NOTES[8]. In 2007 Jacques Marescaux performed the first ever human transgastric cholecystectomy. This was only made possible after rigorous work in live porcine models and human cadavers in the setting of a research program (Anubis Project) which comprised of surgeons, gastroenterologists, computer scientists, and robotic engineers[9].

It is imperative to distinguish that NOTES is not one entity but rather classified as long-range and short-range NOTES. Long-range NOTES refers to traditional NOTES where healthy viscera are dissected to obtain access to a more distant organ, whereas short-range procedure refers to the New NOTES where no viscera are breached to gain access to the target organ[5]. The New NOTES procedures are not limited by the restrictions faced by the long-range NOTES such as difficulties in cutting, hemostasis, suturing, triangulation, closure techniques and spatial orientation[6][10]. From the years of research into traditional NOTES, the submucosal endoscopy with mucosal flap safety valve technique was created in 2007 at Mayo clinic[11]. It aimed to use the submucosa as a potential space for endoscopic applications. This procedure was a milestone as it made way for the application of the first New

NOTES procedure, POEM[11][12]. The growth and advancement of the "New NOTES" in recent years might expand and serve as a bridge for "traditional NOTES"[6].

2. Precursor of the New NOTES: Endoscopic Submucosal Dissection (ESD)

Endoscopic mucosal resection (EMR), the precursor of ESD has been used in gastrointestinal (GI) neoplasms since the early 1980s[13]. ESD is the result of advancement in the field of endoscopy and is now replacing EMR in many areas, mainly because it has overcome hurdles encountered with EMR such as unresectable large tumors and tumors with ulcer scarring[13]. ESD allows en bloc resection of GI lesions. En bloc resection not only makes it possible to assess and detect resection margins, thus helping to make a more adequate histological assessment, but also diminishes post-ESD lesion recurrences in comparison to EMR[14]. However, ESD is technically more demanding and requires a longer procedural time. The major drawbacks of EMR are low radica (Ro)-resection rates and high post–procedure recurrence rates[15]. Park et al[16] reported in their meta-analysis that ESD is significantly more effective than EMR: en bloc resection rates (91.7% vs. 52.1%), complete resection rates (91.9% vs. 43.0%), curative resection and local recurrence rates (0.82% vs. 5.03%). On the other hand, ESD showed inferior outcomes in terms of intraoperative bleeding, perforation risk and operating time. In experienced hands, the benefits of ESD outweigh the risks in comparison to its counterpart, EMR[16].

Originally, indication for ESD was limited to the upper GI tract but has now extended to include colorectal lesions[14]. Several classifications that aim to define the resectability of a lesion by ESD, including Kudo, Paris and NICE classifications have been validated[14]. The most important criteria to consider is the degree of invasion, with only invasion <1000 mm (sm1) into submucosa acknowledged for ESD. Therefore, deeper

are not resectable by ESD and should be sent to surgery because of increased risk of nodal involvement (14% with sm3 lesions, 6% and <1 % for sm2 and sm1 lesions, respectively)[14]. Since endoscopic resection of cancers does not include lymph node dissection, it is imperative to ensure that only lesions with a non-significant risk of lymph node metastasis be resected.

The application of ESD in the context of esophageal tumors is a high risk procedure since the anatomy of the esophagus wall makes it susceptible to a higher risk of lymph node metastasis even in the early stages due to the penetration of lymphatics into the muscularis mucosa layer. As such, the Japanese Esophageal Society Guidelines' absolute indication for ESD are intramucosal esophageal cancers of the epithelium and lamina propria occupying less than 2/3 of the lumen of the esophagus while their relative indication is cancers involving muscularis mucosa or <200-µm invasion of the submucosa[17]. The indication for the use of ESD on the colon has been established by the National Cancer Center in Tokyo and pre-ESD estimation of depth of invasion is carried out using magnifying endoscopes which are seldom attainable in the West[18]. For the stomach, pre-ESD estimation of depth of invasion, the macroscopic type, endoscopic feature, as well as high-frequency endosonographic examination are considered[18].

Despite the fact that ESD is an excellent innovative method for the management of superficial GI neoplasms, further research is warranted to prevent and control post-ESD adverse effects[19].

3. Endoscopic suturing: currently available devices.

Traditional NOTES which originally seemed to bring the best of surgery and endoscopy, a scarless and minimally invasive procedure, came to a halt owing to a lack of a reliable and easy method for defect closure[20]. The original endoscopic suturing devices which were used in NOTES for defect closure of the peritoneal cavity comprised of EndoCinch [Bard, Murray Hill,

NJ], LSI Solution [Victor, NY], and Spiderman [Ethicon Endo Surgery, Cincinnati, OH]. These devices relied on the mechanism of tissue suctioning, after which a needle was passed through the tissue to make the stitch[21]. However, this method was found to be an unreliable solution since most sutures did not have enough depth and were lost at the one year follow-up[22].

Endoscopic suturing devices that are comparable to surgical suturing are the ones that use a curved needle (G-Prox [USGI Medical, San Clemente, CA], Eagle Claw [Olympus Optical LTD, Tokyo, Japan], and Overstitch [Apollo Endosurgery Inc, Austin, TX)[21]. Among those, the only device that is approved for humans in Europe and the USA is the Overstitch [Apollo Endosurgery Inc, Austin, TX]. It can be reloaded as many times as needed without requiring scope withdrawal, such that permanent vision of surgical field is guaranteed[20][23].

As reported by several studies, the Overstitch Apollo suturing device has proved to be a reliable, full thickness suturing device that creates air-tight defect closure that is currently most similar to surgical suturing[21][24][25]. Notably, endoscopic suturing with Overstitch Apollo has become of paramount importance for a new era of the New NOTES procedures.

4. NEW NOTES

4.1. Endoscopic full-thickness resection (EFTR)

Extensive research done in the last 10 years has planted the seeds for the development of EFTR among others. While well investigated techniques like EMR or ESD exist, they are limited to the mucosa and submucosa respectively. Even though mucosal or submucosal resection is satisfactory for the majority of GI lesions, a small portion still require full-thickness

resection and cannot be resected by ordinary techniques due to a high risk of perforation[26].

EFTR is a procedure that allows the radical excision of full-thickness layers of GI tumors, thus permitting resection of GI lesions that originate from or have invaded the muscularis propria, in an en bloc resecting fashion[27][28]. Taking into account infection risk and intraperitoneal dissemination of tumor cells, two types of EFTR methods have been described, namely, exposed and non-exposed EFTR[27]. Unsurprisingly, EFTR leaves a hole in the GI wall, thus the cornerstone of EFTR is a tight defect closure. Two different closure techniques of EFTR described are: 1) Free hands procedure, in which full-thickness resection is done with subsequent defect closure, and 2) Device-assisted EFTR, which consists of firstly securing the GI wall patency and resection afterwards[27].

Being a novel technique, EFTR has no evidence-based or well-established indications to date[29]. Its clinically applicable indications considerably vary in the upper and lower GI tracts. In the upper GI tract the most common indications are subepithelial tumors (SETs) that arise from or invade the muscularis propria. Although not a routine indication due to scarcity of data on duodenal EFTR, non-lifting recurrent or previously untreated non-ampullary duodenal adenomas can also be successfully resected using EFTR. Conversely, the indications of EFTR in the lower GI tract include: incomplete resected non-lifting adenomas, non-lifting adenomas without previous treatment, re-resection of T1-carcinomas, adenomas located in complex anatomical locations not resectable by regular endoscopic resection, such as lesions at a diverticulum and at the appendiceal orifice and SET[27][30][31]. Taking into consideration infection, intraperitoneal metastasis of cancer cells and viscera compression by insufflated CO_2, non-exposed EFTR (Neo-EFTR) is the most minimally invasive technique in comparison to the exposed technique and is deemed the superior technique[27][29].

Since EFTR leaves an opening defect, it is essential to develop a multi-purpose suturing device with equal or comparable air-leak test result as hand-suturing; consequently, a dependable endoscopic suturing device is of paramount importance for the feasibility and safety of the procedure[32]. At present, marketed devices include the Overstitch System (Apollo Endosurgery, Austin, TX, USA), the over-thescope clip (OTSC) (Ovesco Endoscopy GmbH, T€ubingen, Germany) and more recent and sophisticated devices, such as the full-thickness resection device and the double-armed bar suturing system[33]. The development of full-thickness resection devices that are economical, simple to operate and having suturing strength similar to hand-sewn suture, is a difficult task. Moreover, guaranteeing a suitable endoscopic surgical field for suturing and full-thickness resection is another cumbersome task. However, two methods have been described to expand the field of view; one consists of CO_2 gas insufflation and the other expands the field mechanically with surgical retractor with no insufflation required, thus preventing exaggerated pneumoperitoneum[34].

4.2. Per Oral Endoscopic Myotomy (POEM)

Initially received as an investigational procedure, POEM was first described by Inoue et al. in 2008 for the treatment of achalasia in 17 patients after a description of the procedure in animals a few years back[35][36]. Years of research on NOTES has paved the way for the POEM procedure and interestingly, POEM can be regarded as the first and most successful application of NOTES[37]. POEM has revolutionized the management of achalasia by offering a precise myotomy with the advantages of being a scarless procedure[38]. Beyond the original indication, POEM has been applied to a broader target group; including Chicago type 3 spastic achalasia, diffuse esophageal spasm, nutcracker esophagus, jackhammer esophagus and pediatric achalasia in children as young as 3

years old[37][39]. Inoue, Swanström and Stavropoulos described 5 main steps in the procedure: 1) patient positioning and endoscopy planning, 2) access to submucosa, 3) establishing submucosal tunnel 2-3cm below gastroesophageal junction, 4) myotomy, and finally 5) sealing of endoscopic entrance[37][39]. To assess the adequacy of myotomy after POEM, a comprehensive assessment tool is necessary; the Eckardt score seems to be the optimal system in practice[40]. It is calculated by considering four major clinical manifestations: weight loss, dysphagia, retrosternal pain and regurgitation. POEM success is defined as an Eckardt score of less than 3[41].

Hungness et al[42] demonstrated in their series that POEM has similar benefits and outcomes with the more traditional laparoscopic Heller myotomy (LHM), although a shorter operative time (113 vs. 125 min, $p<0.05$) and less blood loss for POEM (≤10 ml in all cases vs. 50 ml, $p<.001$) was reported. Concurrently, another prospective study comparing LHM and POEM by Bhayani et al[43] showed a similar outcome with significantly improved one-month Eckardt scores for POEM and both groups displayed similar improvements in their Eckardt scores at 6 months. Reported advantages of POEM included reduced hospitalisation time, shorter procedure duration and diminished post-procedural solid food dysphagia[43]. Furthermore, the benefit of POEM in a short-term follow-up period of <2 years has clearly been outlined and has been demonstrated to be equal or superior in some aspects (Eckardt score, lower esophageal sphincter (LES) pressure, reduced blood loss, reduced postoperative pain, shorter hospital stay and more rapid resumption of daily life activities) to its traditional counterpart by multiple-studies, including 2 recent meta-analyses, involving more than 1000 patients[44][45][46]. Up to now, no randomised clinical trials comparing LHM and POEM have been published[46].

Unfortunately, published results regarding the long-term benefits of POEM are scarce. The largest report of the

long-term outcomes of POEM with 500 cases was published by Khashab et al[46], who reported significant reduction in Eckardt score and LES pressure and a general success rate of 88.5% in patients followed for a period of at least 3 years.

EndoFLIP (Crospon Medical Devices, Galway, Ireland) is an inflatable balloon currently under investigation as a device that could precisely predict and guide the degree of myotomy which would dramatically improve the outcome of patients requiring POEM and re-treatment[47]. This equipment shows promising capacity; nonetheless, more clinical studies are required to fully assess its use.

Although POEM is positively acclaimed in the short term, further studies are needed to evaluate its long term effects. Powered randomised controlled trials are necessary to compare POEM with LHM to ultimately make it the standard of care for the management of achalasia[44][45][46][48].

4.3. Per Oral Pyloromyotomy (POP)

Growing recognition of POEM has led to the development of per oral pyloromyotomy (POP), previously known as gastric-POEM, and first reported by Kashab et al[49]. This emerging new technique is currently used in patient with gastroparesis refractory to medical therapy and conservative measures. The core technical aspects of POP are somewhat similar to POEM, although POP is technically more difficult to perform due to movement of the antrum and the complexity of properly recognising the pyloric ring. Despite a lack of available data to fundamentally predict its true impact on refractory gastroparesis, earlier studies suggest favorable results, with improving symptoms and a better quality of life for 80% of patients at 3-month follow-up[50]. Although the implementation of POP as the standard treatment for gastroparesis is not yet established due to the intricate pathophysiology of gastroparesis, POP remains an exciting new tool for a disabling disease which has few therapeutic choices[51][52][53].

4.4. Submucosal Tunneling Endoscopic Resection (STER)

Inspired by the POEM procedure, Xu et al[54] used the submucosal tunnel for endoscopical resection and named it STER. The STER procedure can be used for resection of submucosal tumors (SMTs) in the esophagus, the junction between the stomach and esophagus and the stomach. However, due to the challenging anatomy of the stomach, most experts recommend the usage of STER only in the gastric cardia, body, fundus and lesser and greater curvatures[55]. Due to the interference with the visual field and technical difficulty in retrieval of SMTs larger than 3.5cm from the submucosal tunnel and the mouth, they are generally not indicated for STER[56]. The main steps in STER are: 1) a submucosal tunnel is created with a hook knife or hybrid knife 5cm above the tumor, 2) tumor dissection using the same technique as endoscopic submucosal resection, 3) defect closure after mass removal[57].

Zhang et al[58] reported the largest retrospective study on STER involving 290 patients with muscularis propria-originating subepithelial tumors in the upper GI tract. They reported en bloc resection (95.4%) and piecemeal resection (4.6%) with no local recurrence and distal metastases during the follow-up period. They noted a longer operation time for irregular shaped and big tumors and these factors had a negative impact on the en bloc resection rate. They concluded that for upper GI SMTs with a diameter of <3.5 cm, STER was safe and effective. Concurrently, in a study by Chen et al[59], a total of 180 patients with gastrointestinal SMTs who underwent STER were retrospectively analysed to evaluate the long-term outcomes of patients treated with STER. They reported an en bloc resection in 90.6% of patients with a complication rate of 8.3%, without any local recurrences or distant metastases in a median time of 36 months. Risk factors

for complications included large tumor size and irregularly-shaped tumors. All complications were successfully managed with conservative measures. Similarly, a prospective study by He et al[60] including 224 patients with GI SMTs, were treated either with ESD or STER and they achieved an en bloc-resection rate of 92.9%. Although a multi-center, well-devised study exploring long-term outcomes of STER has not yet been done, STER has been shown to be a safe and successful procedure for GI SMTs of <3.5 cm[55].

Some controversies regarding the time required for submucosal tunnel dissection and the appropriate follow-up time are still subjects of discussion. In order to speed up the long process of submucosal dissection, Khashab et al[61] described a new submucosal lifting gel (Cook Medical, Winston-Salem, NC). They reported the gel as auto-dissecting to create a complete submucosal tunnel. The entire procedure without counting tunnel creation was completed in less than 10 minutes. Despite demonstrating encouraging results, larger studies evaluating the long-term effect of this gel are needed[61]. Another controversy in STER is that no optimal follow-up time exists to date. According to Liu et al[56], follow-up strategies after STER should be based on the histology and pathology of the SET with high risk patients followed at a short-term interval compared to non-high-risk patients.

5. New potential applications of submucosa tunneling

One of the intended applications of NOTES was to accurately diagnose conditions previously diagnosed laparoscopically, such as ascites of unknown origin[62]. In 2015, Liu et al[56] invented an esophago-cardial-gastric tunneling (ECGT) peritoneoscopy technique with a flexible endoscope based on the concept of NOTES and POEM for achalasia[63]. This new technique was tried using in vivo dog model to evaluate its safety and efficacy. Based on their results, they concluded that ECGT was a feasible and a promising method for accessing the peritoneum

and reaching a diagnosis[56][63]. Additional studies are needed to confirm its efficacy on humans[56][63].

The first endoscopic diverticulum inversion using the submucosal tunneling technique has also been reported in patients with esophageal epiphrenic diverticula by Liu et al[64]. No recurrence of symptoms was reported in the follow-up period; however larger studies and long-term follow up are needed to confirm the results of this study.

6. Training in New NOTES procedures

STER, POEM and POP are rapidly being adopted worldwide. With that comes a need to properly train those who will in the future perform these procedures[65]. Initially, before undertaking any of the New NOTES procedures, it is essential to be proficient in the precursor ESD techniques, handling of instruments and its principles, to allow the trainees to understand and recognise tissue planes[5]. As such, pre-clinical stimulation plays a vital role in the training for New NOTES procedures; the two most exciting training modalities being ex vivo simulation and virtual reality (VR) NOTES platforms[65].

Gromski et al[66] prospectively analysed the learning curve and effectiveness of ex vivo simulators in colonic ESD training. They noted statistically significant amelioration in colonic ESD performance after 9 colon ESD procedures in ex vivo stimulation. Although a challenging task, Gromski et al[65] are currently building a VR-NOTES simulator called the Virtual Transluminal Endoscopic Surgical Trainer which will be a valuable practicing platform for young "endoscopists".
Stimulation plays a paramount role in the training of NOTES and is expected to decrease the long learning curve for the New NOTES procedures[65].

7. Conclusion

The New NOTES procedures are one the most exciting novel techniques in the last decade. They present an array of

advantages not only for the patients but also for the physicians. In the short term, they have proved to be as advantageous, if not more, in contrast to more conventional operative techniques. Further randomised controlled trials and long-term follow-ups are highly warranted to make the New NOTES the new standard of care.

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