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## Gastrointestinal tract access for urological natural orifice transluminal endoscopic surgery

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### Abstract

We conducted a literature review of natural orifice

transluminal endoscopic surgery (NOTES), focusing on urologic procedures with gastrointestinal tract access, to update on the development of this novel surgical approach. As part of the methods, a comprehensive electronic literature search for NOTES was conducted using PubMed and Cochrane Library from March 2002 to February 2016 for papers reporting urologic procedures performed utilizing gastrointestinal tract access. A total of 11 peer-reviewed studies examining utility of gastrointestinal access for NOTES urologic procedures were noted, with the first report in 2007. The procedures reported in the studies were total/radical nephrectomy, partial nephrectomy, adrenalectomy, and prostatectomy. The transgastric approach was identified in five studies examining total/radical nephrectomy ( $n = 2$ ), partial nephrectomy ( $n = 1$ ), partial cystectomy ( $n = 1$ ), and adrenalectomy ( $n = 1$ ). Six studies evaluated transrectal approach for NOTES, describing total/radical nephrectomy ( $n = 3$ ), partial nephrectomy ( $n = 1$ ), robotic nephrectomy with adrenalectomy ( $n = 1$ ) and prostatectomy ( $n = 1$ ). Feasibility was reported in all studies. Most studies were preclinical and acute, and limited by concerns regarding restricted instrumentation and infection risk. We concluded that gastrointestinal access for urologic NOTES demonstrates promise as described by outlined feasibility studies in preclinical models. Nonetheless, clinical application awaits further advancements in surgical technology and concerns regarding infectious potential.

**Key words:** Gastrointestinal tract; Transrectal; Urology; Natural orifice transluminal endoscopic surgery

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**Core tip:** Gastrointestinal (transgastric and transrectal) access is technically feasible for natural orifice transluminal endoscopic surgery (NOTES) in a number of major urological procedures, and is an attractive alterna-

tive with similar outcomes and distinct advantages compared to transvaginal NOTES. The recent adaptation of robotic technology to transrectal NOTES points the way toward future horizons. Further testing and device development is required prior to clinical application.

Miakicheva O, Hamilton Z, Beksac AT, Berquist SW, Hassan AE, Holden M, Derweesh IH. Gastrointestinal tract access for urological natural orifice transluminal endoscopic surgery. *World J Gastrointest Endosc* 2016; 8(19): 684-689 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i19/684.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i19.684>

## INTRODUCTION

The introduction of minimally invasive urologic surgery has ushered in a new era of surgical advancements that aim to improve surgical outcomes such as decreasing morbidity, expediting patient recovery, and minimizing scars<sup>[1]</sup>. Procedures which were initially laparoscopic, progressed to single-site and robotically assisted minimally invasive techniques and are now made possible *via* natural orifice transluminal endoscopic surgery (NOTES)<sup>[2,3]</sup>.

Indeed, the promise of NOTES has been the next quantum leap of minimally invasive surgery to further decrease wound morbidity and to further diminish the surgical footprint has outcomes associated with traditional laparoscopic surgery. The past ten plus years have seen a dizzying array of feasibility experiments in general surgical, urological and gynecologic natural orifice procedures, with more limited clinical applications. Nonetheless, NOTES currently remains on the margins of surgical practice, restricted to an "avant-garde" of surgical innovators. In urologic practice, NOTES applications have been mostly transvaginal, though given the substantial male patient population, a need to consider alternative points has been imperative. As such, the gastrointestinal tract may present an alternative with greater applicability to the urologic patient population. We conducted a systematic review of the utilization of gastrointestinal tract access in the performance of urological procedures.

## MATERIALS AND METHODS

A systemic electronic literature search was conducted to identify any publications relating to gastrointestinal tract access for urological NOTES using PubMed (<http://www.pubmed.gov/>) and Cochrane Library (<http://www.cochranelibrary.com/>) from March 2002 to February 2016. Several combinations of the following search terms were used to identify pertinent publications: "Natural Orifice Transluminal Endoscopic Surgery", "transrectal", "trans anal", "transgastric", "gastrointestinal tract access", "urology", "NOTES", "nephrectomy", "cystectomy", "adrenalectomy", and "prostatectomy". Only peer-reviewed published series of urological NOTES procedures were included in the analysis of current state

of gastrointestinal tract access urological NOTES. We excluded reviews, editorials, and abstracts.

### Historical context

The coining of NOTES as the exact term was agreed on by the American Society of Gastrointestinal Endoscopy (ASGE) and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Working Group in 2005<sup>[1]</sup>. The first pre-clinical example of natural orifice surgery in urology was completed in 2002 by Gettman *et al*<sup>[4]</sup> when a transvaginal laparoscopic nephrectomy in a porcine model was completed. Since that time, various procedures in urology have been proven possible by NOTES, including partial and radical nephrectomy, cystectomy and prostatectomy<sup>[5]</sup>. Transoral, transgastric, transvaginal, transvesical and transrectal routes have been utilized<sup>[5-7]</sup>. Additionally, NOTES has included various surgical approaches, including laparoscopic and robotic assisted techniques<sup>[5-7]</sup>. Initial barriers to NOTES, outlined by the SAGES/ASGE Working Group<sup>[1]</sup>, included: Access to peritoneal cavity, gastric (intestinal) closure, prevention of infection, development of suturing and anastomotic devices, spatial orientation, development of a multitasking platform to accomplish procedures, management of intraperitoneal complications, physiologic untoward events, compression syndromes, and training. Gastrointestinal tract access NOTES for urologic procedures still remains firmly in pre-clinical research stages; however, there is great potential in extending the availability of NOTES to a greater clinical context. A total of 11 pre-clinical studies utilizing gastrointestinal tract access for NOTES urologic procedures were identified (Tables 1 and 2).

## TRANSGASTRIC UROLOGICAL NOTES

Five studies were identified that investigated utility of transgastric approach for urologic NOTES. Two studies demonstrated feasibility of total nephrectomy, one for partial nephrectomy, partial cystectomy, and adrenalectomy, respectively (Table 1).

### Transgastric nephrectomy and partial nephrectomy

In 2007 Lima *et al*<sup>[8]</sup> first demonstrated feasibility of transgastric access in urologic NOTES for total nephrectomy. This porcine acute study utilized a combined transgastric and transvesical approach *via* an ureteroscope and a gastroscope to successfully perform nephrectomy in all planned procedures ( $n = 6$ ), with median operative time of 120 min. The initial two procedures were notable for mild hemorrhage after renal vessel ligation; however, this was avoided in remaining operations by the application of surgical clips prior to ultrasonic ligation of the vessels. The findings of the study were limited by a lack of closure of gastrotomy due to absence of endoscopic suturing devices and lack of specimen extraction<sup>[8]</sup>.

Isariyawongse *et al*<sup>[9]</sup> investigated utility of NOTES nephrectomy utilizing a hybrid transgastric and trans-

**Table 1 Transgastric gastrointestinal tract access urological natural orifice transluminal endoscopic surgery**

Ref.	Access	Procedures	Model	Summary
Lima <i>et al</i> <sup>[8]</sup> , 2007	Transgastric; transvesical	Nephrectomy ( <i>n</i> = 6)	Porcine	Initial mild hemorrhage appropriately corrected in remaining group
Isariyawongse <i>et al</i> <sup>[9]</sup> , 2008	Transgastric; transvaginal	Nephrectomy ( <i>n</i> = 1)	Porcine	Successful bilateral nephrectomies achieved with both transvaginal and transgastric approaches
Sawyer <i>et al</i> <sup>[12]</sup> , 2009	Transgastric; transurethral	Partial cystectomy ( <i>n</i> = 5)	Porcine	Successful completion of pure transurethral NOTES transurethral ( <i>n</i> = 4) and pure transgastric NOTES ( <i>n</i> = 1)
Boylu <i>et al</i> <sup>[10]</sup> , 2010	Transgastric; hybrid	Partial nephrectomy ( <i>n</i> = 1)	Porcine	Use of thulium laser in successful partial nephrectomy
Fritscher-Ravens <i>et al</i> <sup>[11]</sup> , 2008	Transgastric	Adrenalectomy ( <i>n</i> = 10)	Porcine	A comparative study of NOTES alone <i>vs</i> NOTES and endoscopic ultrasound guidance NOTES

NOTES: Natural orifice transluminal endoscopic surgery.

**Table 2 Transrectal gastrointestinal tract access urological natural orifice transluminal endoscopic surgery**

Ref.	Access	Procedures	Model	Summary
Bazzi <i>et al</i> <sup>[13]</sup> , 2011	Transrectal hybrid	Nephrectomy ( <i>n</i> = 3)	Porcine	First report of transrectal hybridized NOTES
Bazzi <i>et al</i> <sup>[15]</sup> , 2012	Transrectal hybrid	Nephrectomy ( <i>n</i> = 4)	Cadaver	Successful nephrectomy in a cadaveric model with intact specimen extraction
Eyraud <i>et al</i> <sup>[18]</sup> , 2013	Transrectal hybrid	Robot assisted nephrectomy and adrenalectomy ( <i>n</i> = 1)	Cadaver	First investigation of robotic nephrectomy and adrenalectomy. Successful adaptation of robot to NOTES platform
Bazzi <i>et al</i> <sup>[17]</sup> , 2013	Transrectal hybrid; Transvaginal hybrid	Partial nephrectomy ( <i>n</i> = 10)	Porcine	No significant in access or operative times for transrectal or transvaginal approaches to partial nephrectomy
Park <i>et al</i> <sup>[16]</sup> , 2014	Transvaginal; transrectal; Conventional laparoscopy	Nephrectomy ( <i>n</i> = 15)	Porcine	Survival model; no difference in evidence of infection or injury at necropsy; no difference in inflammatory markers
Akça <i>et al</i> <sup>[19]</sup> , 2015	Transrectal	Prostatectomy ( <i>n</i> = 1)	Cadaver	Proof of principle for transrectal approach for NOTES prostatectomy

NOTES: Natural orifice transluminal endoscopic surgery.

vaginal approach. Successful bilateral nephrectomy was performed by first visualizing the abdominal cavity *via* a transgastric endoscope and using the transgastric endoscope to establish a transvaginal NOTES port. Total operative time was 40 min for the right nephrectomy and 20 min for the left. The combined transgastric-transvaginal approach allowed for excellent visualization, multitude of readily available instruments to perform basic surgical tasks, and successful specimen extraction through a transvaginal route<sup>[9]</sup>.

Boylu *et al*<sup>[10]</sup> successfully demonstrated the feasibility of transgastric NOTES partial nephrectomy hemostasis in the porcine model. The procedure utilized a therapeutic gastroscope (Olympus GIF-2T160, Melville, NY, United States) combined with a thulium laser (RevoLix; AllMed Systems, Pleasanton, CA, United States) to gain access to the peritoneum, visualize and complete excision the left kidney's upper pole without additional hemostatic measures. The specimen was extracted using an endoscopic wire loop *via* the stomach and the gastrostomy was closed with metal clips. Total operative time was 240 min. Limitations described by the authors included excess smoke produced by the thulium laser as well as lack of appropriate entrapment sacks for safe specimen removal *via* a gastroscope<sup>[10]</sup>.

**Transgastric adrenalectomy**

Fritscher-Ravens *et al*<sup>[11]</sup> demonstrated adrenal gland removal in pigs using NOTES alone or with endoscopic ultrasound guidance (EUS). The study showed that

adrenal gland removal failed in all NOTES-only procedures (*n* = 4) in which it was attempted while it was successful in six NOTES-EUS (*n* = 6) cases. The NOTES-only cases of adrenalectomy were halted due to lack of safe access to the organ and bleeding during attempted access. Successful adrenalectomy was achieved in the NOTES-EUS group without complication with a mean duration of 78 min. In addition to successful adrenalectomy in the combined NOTES-EUS approach, the study demonstrated successful closing of the gastrostomy using an endoscopic suturing system<sup>[11]</sup>.

**Transgastric partial cystectomy**

NOTES partial cystectomy in a porcine model was described by Sawyer *et al*<sup>[12]</sup>. The study outlined both two approaches: Transgastric with a urethral assist port and pure transurethral. Both approaches allowed for the completion of successful partial cystectomy with specimen excision and defect reapproximation with endoscopic clips. Transgastric partial cystectomy was performed in one porcine model with an operative time of 93 min. The authors noted that despite being more invasive, the transgastric approach offered better visualization of target anatomy and ability to sample lymph nodes for malignant pathology<sup>[12]</sup>.

**TRANSRECTAL UROLOGIC NOTES**

Six studies investigated utility of transrectal NOTES for urologic procedures. Three studies demonstrated

feasibility of total nephrectomy, one for partial nephrectomy, total nephrectomy and adrenalectomy, and prostatectomy, respectively (Table 2).

### **Transrectal NOTES nephrectomy**

Bazzi *et al.*<sup>[13]</sup> described the first transrectal NOTES nephrectomy in an acute porcine model utilizing a transrectal access technique described by Ramamoorthy *et al.*<sup>[14]</sup>. This form of access involved creation of a submucosal tunnel in the anus, and dissection along the posterior rectal wall and access into the retroperitoneum, which was monitored by a transumbilical port which was also used for additional retraction, thus fitting into the "hybrid" NOTES model. Three cases of transrectal hybrid NOTES nephrectomy were successfully completed without conversion to conventional laparoscopic or open surgery and without significant intra-abdominal bleeding. Median operative time was 180 min and estimated blood loss was < 50 mL for all cases. The setting of a transrectal access with nephrectomy provided the advantages of a larger access point for instruments and specimen retrieval, easier closure of the access site compared to the transgastric approach, and the ability for application of the approach in both sexes, compared to transvaginal access. The success of this initial report provided proof-of-principle for the transrectal approach as an alternative to the primary transvaginal approach<sup>[13]</sup>.

Bazzi *et al.*<sup>[15]</sup> described feasibility of transrectal hybrid NOTES nephrectomy in four human cadavers. Similar to prior work, the hybrid approach utilized a periumbilical transabdominal laparoscopic port. All four cases were performed successfully with a mean operative time of 175 min and no conversions of operative approach. The periumbilical port was utilized for guidance of transrectal access, assistance in renal mobilization, and in deployment of the stapler. However, more than 75% of the procedure was performed *via* instrumentation inserted *via* the transrectal access<sup>[15]</sup>.

Park *et al.*<sup>[16]</sup> compared feasibility and safety of transrectal ( $n = 5$ ), transvaginal ( $n = 5$ ) and conventional laparoscopic ( $n = 5$ ) total nephrectomy in a survival porcine model, and examined inflammatory cytokines between the groups. They noted that all procedures were successfully completed without conversion, and while operative time was longer for transrectal and transvaginal approaches (84 min vs 61 min vs 24 min, respectively,  $P < 0.001$ ), there were no signs of visceral injury or peritonitis on postmortem examination at the 1 wk mark. Furthermore, none of the laboratory parameters, including white blood cell count, tumor necrosis factor- $\alpha$ , interleukin (IL)-1, and IL-6 differed among the groups during the entire experimental period<sup>[16]</sup>.

### **Transrectal NOTES partial nephrectomy**

Bazzi *et al.*<sup>[17]</sup> compared transrectal ( $n = 5$ ) and transvaginal ( $n = 5$ ) approaches for hybrid NOTES partial nephrectomy in an acute porcine model. In this study, 10 porcine models (5 transrectal, 5 transvaginal) un-

derwent partial nephrectomy. Following transrectal and transvaginal access, the SPIDER (Transenterix, Morrisville, NC, United States) articulating dissecting and suturing platform, was deployed. The procedure was completed successfully in all 10 cases without need for conversion. There were no significant differences when comparing transrectal and transvaginal approaches for access time (29.2 min vs 29.6 min,  $P = 0.944$ ), operative time (196 min vs 183 min,  $P = 0.631$ ) or estimated blood loss (59 mL vs 54 mL,  $P = 0.631$ )<sup>[17]</sup>.

### **Transrectal NOTES robotic nephrectomy and adrenalectomy**

Eyraud *et al.*<sup>[18]</sup> demonstrated feasibility of robotic (Da Vinci SI, Intuitive Surgical, Sunnyvale, CA, United States) assisted hybrid transrectal NOTES nephrectomy and adrenalectomy in a male cadaver. Transrectal access was achieved by a submucosal tunnel followed by placement of a robotic 8 mm-trocar. This was followed by placement of periumbilical 12 mm and 8 mm robotic ports, and a transrectal 8 mm robotic ports. The procedure was successfully completed with an operative time of 145 min, of which 20 min was for access/robotic docking and 20 min was for rectal closure<sup>[18]</sup>.

### **Transrectal NOTES prostatectomy**

Akca *et al.*<sup>[19]</sup> described transrectal NOTES prostatectomy in a cadaveric model. The cadaver was placed in an exaggerated lithotomy position, the anterior rectal wall was incised, and a single port device (GelPOINT®, Applied Medical, Santa Margarita, CA, United States) was deployed, through which all working and camera ports were inserted through. The authors reported ease of exposure of the posterior surface of the prostate and seminal vesicles with intact specimen extraction, and pointed the way for further testing with respect to feasibility of lymph node dissection using the transrectal route<sup>[19]</sup>.

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## **FUTURE DIRECTIONS**

In order for transrectal NOTES to evolve into a clinically viable option, advances in device development and addressing concerns regarding infection risk with outcomes comparable to conventional laparoscopy must be demonstrated<sup>[20]</sup>. Single port surgery can lead to reduced maneuverability and difficult laparoscopic suturing skills, thus further developments will likely incorporate robotic platforms to overcome these limitations<sup>[21]</sup>. Transrectal NOTES has continued to gain influence in the setting of colorectal surgery, and further advancement in urology will require emulation of this field<sup>[22]</sup>. From this foundation of colorectal procedures, urologic applications can continue to advance.

Robotic assistance in NOTES has been suggested as a way to increase surgical feasibility and procedure applicability<sup>[23]</sup>. As the robotic platform continues to expand in its scope of utilization in urologic surgery,

applications of robotics in NOTES may follow. As robotic technology continues to evolve in the direction of decreased instrument profile and flexible articulation, haptic feedback and improved optics, robotic NOTES may reach that critical tipping point of fusion of technical feasibility, adoption, desirability by patients and ultimately, acceptance by medical and surgical establishments to enter the mainstream of the surgical armamentarium.

Concerns regarding infectious potential of transiting viscera have been a significant hindrance to acceptance and application of NOTES, and this is especially true with the transrectal approach. Given high bacterial prevalence in the gastrointestinal tract, post-operative infections continue to be a major concern regarding transrectal NOTES<sup>[24]</sup>. Device innovation is working to decrease this risk as well. Recently, Senft *et al.*<sup>[25]</sup> demonstrated the efficacy of ColoShield (A.M.I., Feldkirch, Austria), a colon occlusion device, in reducing peritoneal contamination in transrectal NOTES. The occlusion device is inserted 15-20 cm above the anus, inflated to ensure a tight seal with the colonic wall, and maintained in the position through the duration of the surgery. The device acts as a physical impediment in the colon to prevent any unwanted fecal contamination. Device innovations such as this will certainly play a role in the future of transrectal NOTES.

## CONCLUSION

Transvaginal NOTES, although feasible for urologic procedures, has limited applicability to the female population<sup>[26]</sup>. The introduction and exploration of gastrointestinal tract as a urological NOTES entry site opens up the realm of the minimally invasive technique to a much larger population. Urologic transrectal and transgastric NOTES has thus far included nephrectomy, partial nephrectomy, adrenalectomy, and prostatectomy, as well as robotic-assisted techniques. Future pre-clinical survival studies are requisite to determine the potential of urologic transrectal NOTES, with emphasis on improved instrumentation, robotic assistance, and avoidance of infection.

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## Microvasculature of the esophagus and gastroesophageal junction: Lesson learned from submucosal endoscopy

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### Abstract

Advanced therapeutic endoscopy, in particular endoscopic mucosal resection, endoscopic submucosal dissection, per-oral endoscopic myotomy, submucosal endoscopic tumor resection opened a new era where direct esophageal visualization is possible. Combining these information with advanced diagnostic endoscopy, the esophagus is organized, from the luminal side to outside, into five layers (epithelium, lamina propria with lamina muscularis mucosa, submucosa, muscle layer, adventitia). A specific vascular system belonging to each layer is thus visible: Mucosa with the intra papillary capillary loop in the epithelium and the sub-epithelial capillary network in the lamina propria and, at the lower esophageal sphincter (LES) level with the palisade vessels; submucosa with the drainage vessels and the spindle veins at LES level; muscle layer with the perforating vessels; peri-esophageal veins in adventitia. These structures are particularly important to define endoscopic landmark for the gastro-esophageal junction, helpful in performing submucosal therapeutic endoscopy.

**Key words:** Microvasculature; Esophageal anatomy; Submucosal endoscopy; Per-oral endoscopic myotomy; Advanced imaging

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**Core tip:** In the last years advanced endoscopic technology and techniques allowed the possibility to *in vivo* evaluate the esophageal vasculature. We aimed to

review the endoscopic endoluminal and transluminal appearance of the esophageal vascular structures. This paper will allow the reader to deeply understand mucosal, submucosal and muscular layer vessels by a direct endoscopic visualization. The authors' knowledge of the characteristic changes in health and disease, as well as descriptions of anatomical landmarks, will serve to inform the practice of endoscopic surgery in the future.

Maselli R, Inoue H, Ikeda H, Onimaru M, Yoshida A, Santi EG, Sato H, Hayee B, Kudo SE. Microvasculature of the esophagus and gastroesophageal junction: Lesson learned from submucosal endoscopy. *World J Gastrointest Endosc* 2016; 8(19): 690-696 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i19/690.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i19.690>

## INTRODUCTION

Flexible endoscopes were first introduced in 1950s and since that time physicians have been able visualize the gastrointestinal tract. In the past 10 years endoscopy benefited from several technologies such as high-definition television, high-resolution endoscopy, magnification and narrow band imaging (NBI)<sup>[1]</sup>. Results from the anatomical *ex-vivo* studies have informed the approach to endoscopic examination, but these technologies herald a new era of observation, where the direct visualization of living tissue can confirm, and add to, the observations of the past.

In this article we aimed to review the endoscopic endoluminal and transluminal appearance of the esophageal vascular structures, with particular attention to the state-of-the-art endoscopic equipment and techniques now available.

### **Advanced diagnostic endoscopy: Magnification endoscopy and NBI**

Magnification endoscopy up to 80x (GIF-H260, Olympus Medical Systems Co. Tokyo, Japan) is an excellent tool for the visualization of the normal esophageal mucosa and in the diagnosis of early esophageal cancer<sup>[2]</sup>. Using magnification, one can begin to visualize the esophageal microvasculature, with the surface capillaries displaying a looped configuration<sup>[3]</sup>: The intra-papillary capillary loops (IPCLs).

NBI is a relatively recent modality employing narrow-bandwidth filters [red-green-blue (R/G/B) sequential system]<sup>[4]</sup>, to increase the contrast between the mucosal surface and the underlying vascular pattern<sup>[5]</sup>. The depth of penetration, and thus the color seen in the screen, depends on the wavelength used: It is superficial for the blue band, deep for the red band and intermediate for the green band. The blue filter in particular has been designed to be similar to the peak absorption of hemoglobin, in order to emphasize capillary vessels at

the mucosal surface<sup>[6]</sup>. Magnification endoscopy with NBI (M-NBI), therefore, has been developed for two distinct applications: The analysis of the architecture of the epithelium (or microsurface) and analysis of the microvasculature<sup>[7]</sup>.

### **Advanced diagnostic endoscopy: Endocytoscopy and Endomicroscopy**

New optical imaging modalities to enable *in vivo* characterization of suspicious lesions involves both endogenous optical contrast as well as the use of contrast agents targeted against biomarkers that are associated with early and superficial neoplasias<sup>[8]</sup>.

Recently the confocal laser endomicroscopy (CLE) has been studied in the evaluation of the gastrointestinal (GI) tract. Fluorescence diagnosis can be achieved by measuring the tissue fluorescence following administration of an agent (usually fluorescein).

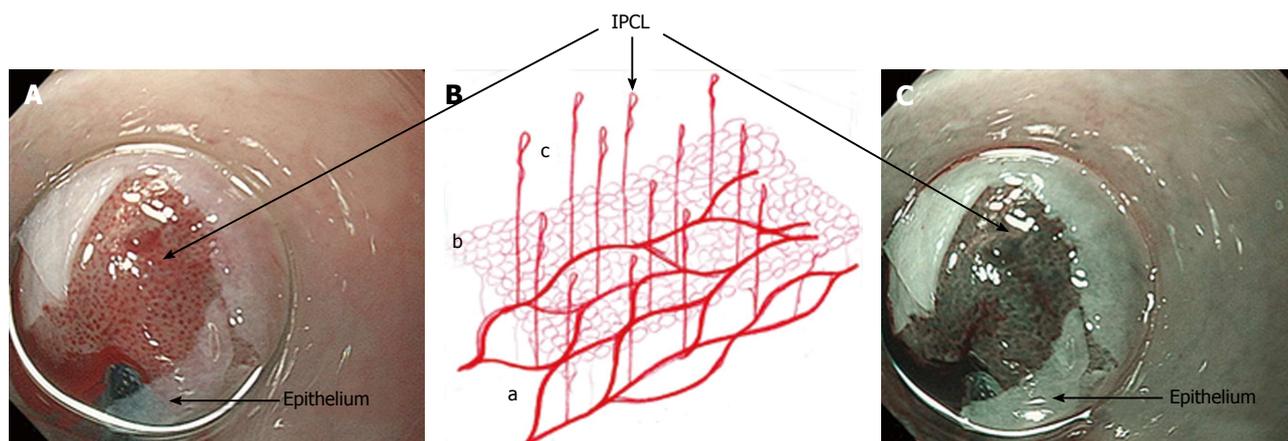
The typical resolution achievable with CLE is on the order of 1-2  $\mu\text{m}$  with a field of view of approximately 500-700  $\mu\text{m}^2$ . It allows for the immediate evaluation of the superficial GI layers and can be used for morphological diagnosis because of the recognition of morphological changes in cells and nuclei<sup>[9]</sup>.

Several studies have compared the performance of confocal microendoscopy to white light endoscopy examination and NBI in the esophagus and colon. In particular in the esophageal field, most of these papers were focused on Barrett Esophagus changes.

More recently the endocytoscopy was introduced. A prototype gastroscope (Olympus Medical Systems Corp., Tokyo, Japan) with a high-power magnifying endocytoscope (450  $\times$  magnification) was used to compare the size and appearance of nuclei and cytoplasm ratio, without the need of a contrast agent. In the esophagus the endocytoscopic images has been classified into five grades of endocytoscopic atypia (ECA) from healthy squamous epithelium (ECA 1) to lesion recognized as malignant (ECA 5)<sup>[10]</sup>.

### **Advanced therapeutic endoscopy**

Advanced operative endoscopy, ranging from endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), per-oral endoscopic myotomy (POEM), submucosal endoscopic tumor resection (SET), has open the door to the direct view of the submucosal virtual space and its anatomy. If with diagnostic endoscopy the interest was related only in understanding "superficial" findings and in wondering the submucosal subsequent meanings, the current procedures let the physician to watch from "inside" with his/her eyes a real, true anatomy of submucosal space, until now only imagined by both diagnostic endoscopists and surgeons. EMR and ESD are performed as indicated by local clinical guidelines for early esophageal cancers, POEM for esophageal achalasia<sup>[11-15]</sup> and SET for subepithelial tumors<sup>[16]</sup>. These procedures enable clear and direct visualization of the layers of the esophageal wall, as therapy progresses.



**Figure 1 Mucosal vessels.** A and C: Endoscopic images during per-oral endoscopic myotomy procedure (high magnification images); after unintentional removal of the epithelium (white layer), top half of epithelium was peeled off, and IPCLs were exposed. IPCLs appear as regularly-arranged, red dots (A: White light) or dark green spots (C: NBI); B: A schematic representation of the vascular network of esophageal mucosa: a: Branching vessels; b: SECN; c: IPCL. IPCL: Intrapapillary capillary loop; SECN: Sub epithelial capillary network; NBI: Narrow band imaging.

### Esophageal vasculature: Endoscopic appearance

Combining the information gained from the therapeutic endoscopy, the esophageal wall is organized, from the lumen to outside, in five different layers: Epithelium, lamina propria with lamina muscularis mucosa, submucosa, muscle layer, adventitia. Different vascular system are recognize, belonging to each layer and connecting each other: In the mucosal layer we can find IPCL in the epithelium and sub-epithelial capillary network (SECN) in the lamina propria (Figure 1); at the lower esophageal sphincter (LES) level, we can recognize palisade vessels running in this layer; in the submucosa we find drainage vessels and the spindle veins just under the LES; in the muscle layer are present perforating vessels and peri-esophageal veins in Adventitia. In particular, considering the vasculature by each layer we can find the following structures (Figure 2)<sup>[16]</sup>.

**Mucosa:** IPCLs and the SECN can be visualized laying all along the esophagus, from the upper esophageal sphincter (UES) to the LES (Figure 3). IPCLs are terminal vessels laying in the epithelial papilla and they drain into the branching vessels located within the lamina propria; they can be clearly demonstrated with M-NBI, although they are visible even with magnification alone. The branching vessels finally drain into the submucosal drainage vessels.

**Submucosa:** It is a connective “space” between the mucosa and the muscle layer. In this layer drainage vessels can be found running in the entire esophageal length; at the esophagogastric junction (GEJ) level the drainage veins become elongated.

**Muscle layer:** It is a double layer composed by muscular fibers running circularly in the inner layer and longitudinally in outer part. It is crossed by a venous network running in the intramuscular space. The muscle

layer is also crossed by additional perforating vessels, large veins connecting the submucosal drainage veins/arteries with the main longitudinal arteries and veins of the adventitia, the outer esophageal layer.

**Adventitia:** It is the outermost connective tissue layer, enclosing the esophagus in all its length. The peri-esophageal vessels are clearly demonstrated during submucosal endoscopy for POEM, after the myotomy.

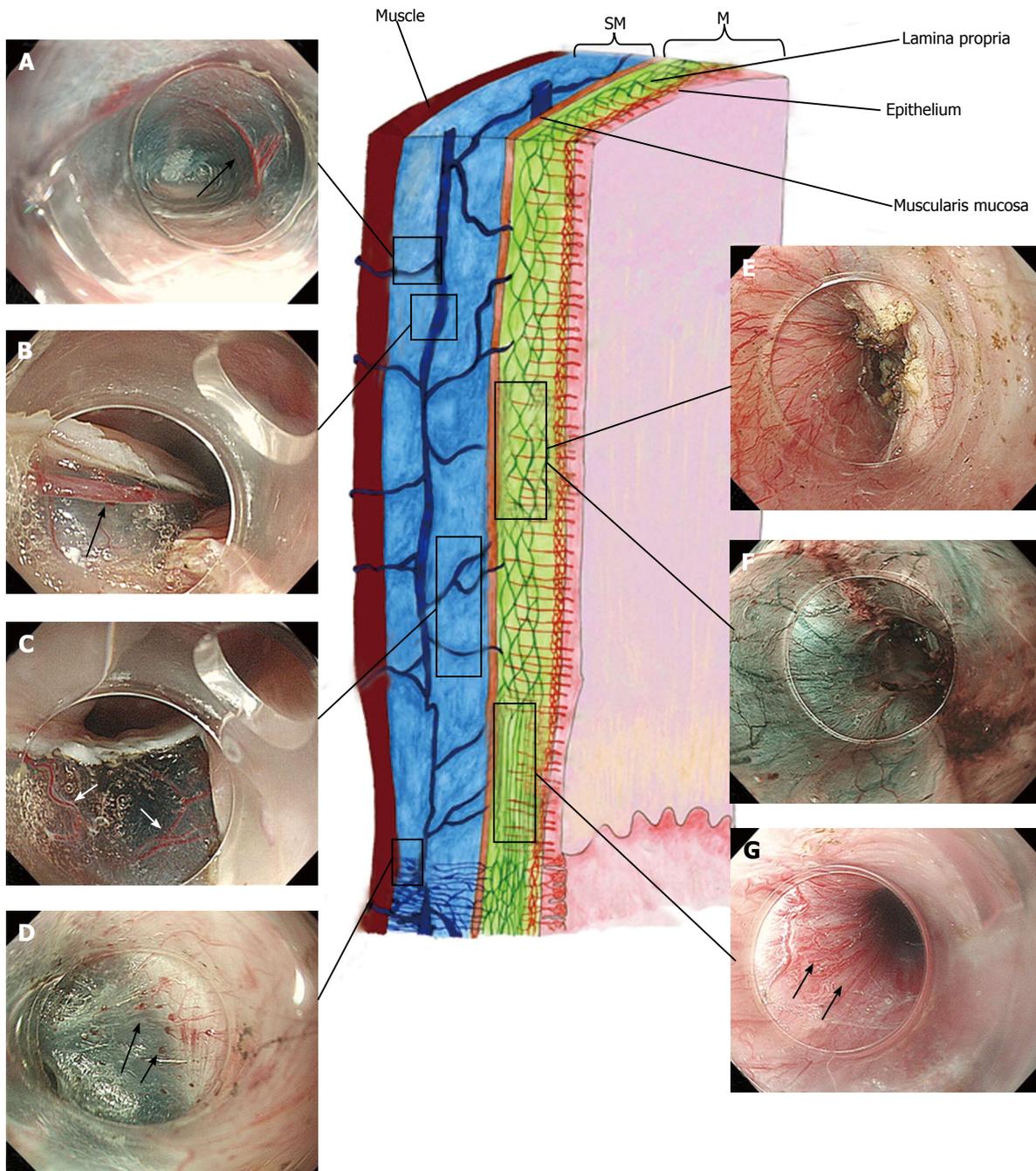
From the early 90s several studies focused on IPCL changes relevant to malignant tumors<sup>[2]</sup>. These studies led to the development of the IPCL classification<sup>[1]</sup>: IPCLs show characteristic changes in carcinoma *in situ* (irregular caliber, weaving, dilatation and different shape of IPCL). Analyzing grades of IPCL changes, the mucosa can be differentiated from normal (Type I) to carcinoma (Type V). By this classification, infiltration depth of the esophageal lesion can also be evaluated.

## ESOPHAGEAL VASCULATURE ON HISTOLOGY

The immunohistochemical analysis on non-pathological esophageal specimens using CD34, specific for the vascular endothelium, and D2-40, specific for lymphatics, shows a high expression of CD34 in the areas corresponding to the IPCLs, SECN and branching vessels (Figure 4). IPCLs and SECN stained with CD34, but they are negative for D2-40 staining.

## GEJ: ENDOSCOPIC LANDMARKS

The GEJ is usually endoscopically defined as that area where the palisade vessels encounter gastric longitudinal mucosal folds<sup>[17-19]</sup>. These structures can be directly seen by entering in the submucosal space: From this internal point of view, on the mucosal side, the branching vessels appears neighboring with palisade vessels, running in the



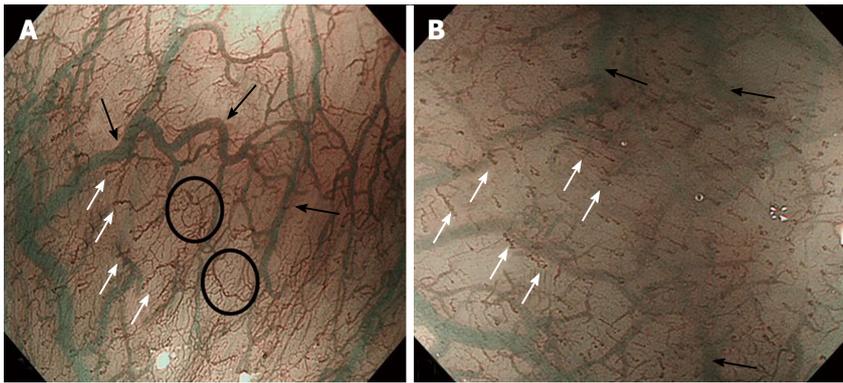
**Figure 2 Esophageal wall and esophago-gastric junction vasculature: Schematic illustration and endoscopic corresponding images (high magnification images).** Black arrow indicates vessels. This image was originally published in "Treatment Strategies Gastroenterology"<sup>[26]</sup>. A: Perforating vessels from the outer esophagus to the submucosal vessel; image captured during tunnelization in POEM (bottom side muscle layer, left side submucosal lifting); B: Submucosal drainage vessel (mucosal layer lifted on during ESD). These veins can become esophageal varices in portal hypertension; C: Submucosal vessels connecting the drainage veins to the mucosal branching vessels (in the lamina propria); D: Spindle veins immediately below the GEJ (in left side of the image, in blue, the submucosa and in the right side the muscle); E and F: Whitet light and NBI of the branching vessels (seen from inside the submucosal tunnel). Backside of the mucosa on the left; muscle-already cut-on the right; G: Passage between lower esophagus and GEJ. In the image is possible to recognize, in different planes, all the vessel of the submucosa and lamina propria (palisade vessels). POEM: Per-oral endoscopic myotomy; ESD: Endoscopic submucosal dissection; GEJ: Esophagogastric junction; NBI: Narrow band imaging; M: Mucosa; SM: Submucosa.

same plane, just above the muscularis mucosae.

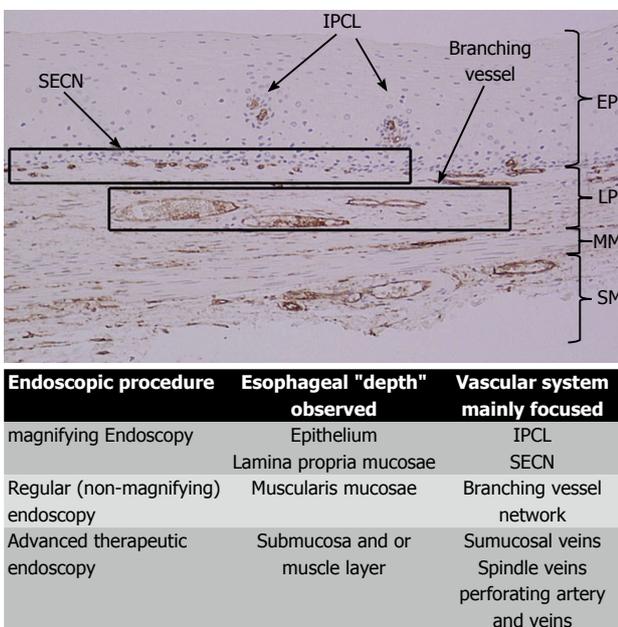
In the submucosal layer, immediately below the GEJ, small veins are laying, running regularly and parallel to each other, perpendicularly to the muscular layer, found in most of the patients (Figure 5). These "spindle veins" can be considered a reliable landmark of the GEJ already been passed through.

## DISCUSSION

The first descriptions of the esophageal vasculature and its connection with the portal system span from Vesalius in 1543 to Bartholin in 1673 and Dionis in 1703. In 1951 Butler recorded a more detailed description, categorizing the intramural esophageal vessels into intrinsic veins,



**Figure 3** High magnifying narrow band imaging image of normal esophageal mucosa (luminal side). A: Soft pressure of the endoscope distal attachment ("hood") onto the mucosal surface demonstrates SECN, hard pressure onto the mucosa compresses horizontal vessels, allowing clear observation of IPCLs; B: In the circle the SECN located at the top layer of lamina propria mucosae, just beneath the epithelium. The black arrows indicate the branching vessels into the lower lamina propria; white arrows indicate the IPCL located in the epithelial papilla, which is a projection of lamina propria mucosae into the epithelium. SECN: Sub-epithelial capillary network; IPCL: Intrapapillary capillary loop.



**Figure 4** The figure shows the histology of a non-pathologic esophageal specimen. The vessels' wall has been colored by CD34, showing superficially the IPCLs (upper part of the lamina propria, arising the epithelium) and the SECN; deeply in the lamina propria the branching vessels. In the sumucosal layer also the drainage veins are evident. The table summarizes the vascular system observed and its own esophageal layer according to the different endoscopic procedure performed. SECN: Sub-epithelial capillary network; IPCL: Intrapapillary capillary loop; EP: Epithelium; LP: Lamina propria; MM: Muscularis mucosa; SM: Submucosa.

venae comitantes of the vagus and extrinsic veins<sup>[20]</sup>.

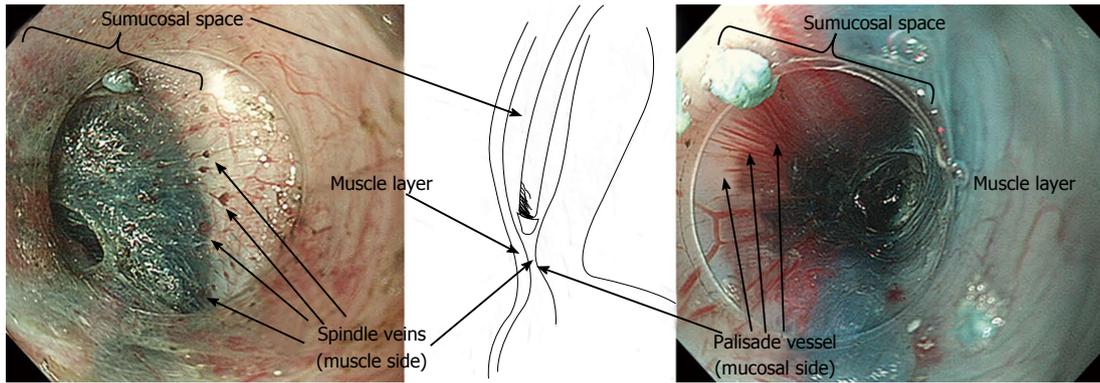
Subsequent descriptions have concentrated largely on abnormalities due to esophageal varices, but these were limited to post-mortem, *ex vivo* analysis, frequently employing the corrosion-cast technique, or scanning electron microscopy (visualizing vessels down to 200  $\mu\text{m}$ )<sup>[21]</sup>. These studies demonstrated the existence of a SECN, a draining submucosal venous plexus, and the anastomoses between these two.

Advanced therapeutic endoscopy allows, for the first time, the direct *in vivo* observation of the deeper

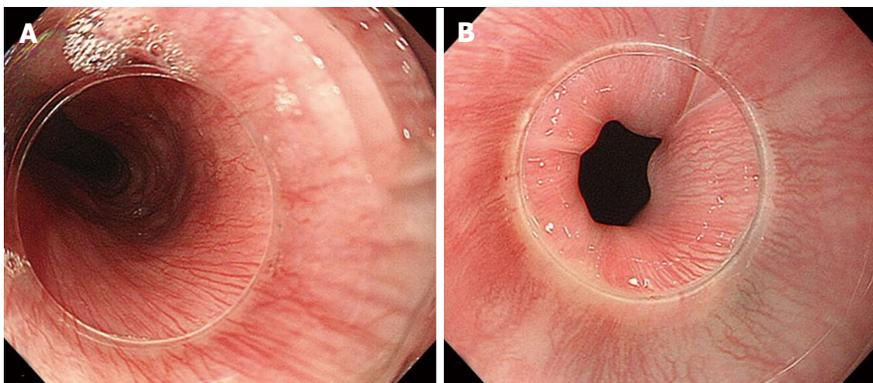
layers of the esophageal wall. Many of these structures are of interest and key importance to endoscopists undertaking advanced therapeutic procedures.

Previous studies of the esophageal vasculature have yielded conflicting observations. Palisade vessels were first described using microangiography, then in 1984 endoscopically identified as "sudare-like veins"<sup>[19]</sup>. In 1987 Vianna *et al*<sup>[22]</sup> performed a study on the normal esophageal venous circulation and defined in particular the palisade zone located at the gastroesophageal junction. The veins in this zone were distributed uniformly, running longitudinally and parallel to each other. The submucosal veins of the gastric zone were described as piercing the muscularis mucosae at the GEJ, running in the lamina propria, with the exception of a small number which seemed to remain in the submucosal space<sup>[22]</sup>. In contrast, Aharinejad *et al*<sup>[23]</sup> demonstrated that submucosal veins maintain their general longitudinal course when passing through the GEJ. Using M-NBI, Kumagai and colleagues observations of the GEJ and its vessels corresponded to the *ex vivo* description of Kagaries and Butler: They described in the lamina propria a longitudinal plexus of small vessels and in the submucosa at the GEJ, the palisade vessels, with a caliber of 150-170  $\mu\text{m}$ . They demonstrated that the density of palisade vessels is highest near the squamo-columnar junction and that starting from their proximal ends they gradually increase in thickness and become confluent<sup>[24]</sup>. Using M-NBI, our endoscopic findings, approaching the submucosal space, correspond most closely to those of Aharinejad, with the palisade vessels at the GEJ lying in the lamina propria. In other words, the palisade vessels are continuations of the branching vessels, but we postulate that the vessels appear elongated as a result of the high pressure forces present at the GEJ. This is supported by the presence of similar vessels at the UES level (Figure 6).

The GEJ has previously been divided into four distinct zones (the first two immediately below and the second two above the "Z" line). In zone 1, the most caudally zone directly connected with the gastric side, a complex



**Figure 5** In the center a scheme of the submucosal view at the gastro-esophageal junction during per-oral endoscopic myotomy. At the muscle side (left endoscopic image) the spindle vein are clearly visible; at the mucosal side (seen on its backside, right endoscopic image) the palisade vessel are recognized. High magnification images.



**Figure 6** Palisade vessels at the esophageal sphincter. A: Palisade vessels at the upper esophageal sphincter; B: In the lower esophageal sphincter, the vessels, located in the lamina propria, are continuation of the branching vessels, "stretched" by the high pressure present in the area. High magnification images.

of small twisted veins, with circumscribed, ampullar bulges<sup>[21]</sup> - has been found. These veins correspond to the so-called "spindle veins", found in more than 70% of the total cases of our personal series and clearly visible during submucosal endoscopy.

The architecture of IPCLs has been evaluated *ex vivo* in the normal esophagus, with microfilm<sup>[19]</sup>; comparing these stereoscopic microscopic images with magnifying endoscopic images, at a magnification of approximately 80 times, small vessels coming up from the mucosal vessels could be seen originating and running obliquely upward toward the epithelium and then toward to the intrapapillary capillaries. At a magnification of more than 100 × each intrapapillary capillary can be observed as a single distinct loop<sup>[25]</sup>.

As endoscopists have become more familiar with M-NBI, it became apparent that characteristic morphological changes were associated with the development of malignancy<sup>[26]</sup>. These observations finally led to the development of the IPCL classification<sup>[1,27]</sup>.

Esophageal vasculature is now *in vivo* evaluable with advanced endoscopic technology and techniques. Our knowledge of the characteristic changes in health and disease, as well definition of anatomical landmarks, will serve to the practice of endoscopic diagnostics and treatment in the future.

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## Observational Study

## Patients presenting for colonoscopy: A great opportunity to screen for sleep apnea

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### Abstract

#### AIM

To discover the prevalence and the feasibility of screening for obstructive sleep apnea (OSA) in patients presenting for routine colonoscopy.

#### METHODS

Adult patients having a colonoscopy for routine indications at our outpatient endoscopy center were eligible if they did not carry a diagnosis of OSA or had not had a prior sleep study. All patients were administered the Berlin questionnaire prior to the procedure. Mallampati, neck circumference, height, weight, and BMI were obtained for each patient. Patients were observed for any drops in oxygen saturation < 92% or the presence of snoring for > 10 s. Patients were determined to be high-risk if they met at least 2 of the 3 symptom categories for the Berlin questionnaire.

#### RESULTS

A total of 60 patients were enrolled and completed the study; mean age was 56 years (range 23-72 year). Twenty-six patients had a positive Berlin questionnaire (43.3%), 31 patients had a negative Berlin questionnaire (51.6%) and 3 patients had an equivocal result (5.0%). Patients with a positive Berlin questionnaire were more likely to be of increased weight (mean 210.5 lbs vs mean 169.8 lbs,  $P = 0.003$ ), increased BMI (33.0 kg/m<sup>2</sup> vs 26.8 kg/m<sup>2</sup>,  $P = 0.0016$ ), and have an increased neck circumference (38.4 cm vs 35.5 cm,  $P = 0.012$ ).

Patients with a positive Berlin questionnaire were more likely to have a drop in oxygen saturation < 92% (76.9% *vs* 36.4%,  $P = 0.01$ ). Patients with snoring were more likely to have a positive Berlin questionnaire (8/9 patients *vs* 1/31 patients with negative Berlin questionnaire;  $P = 0.0045$ ).

### CONCLUSION

Risk for OSA is extremely common in a population presenting for a routine colonoscopy, and screening at the time of a colonoscopy offers an excellent opportunity to identify these patients.

**Key words:** Colonoscopy; Obstructive sleep apnea; Berlin questionnaire; Sedation; Screening

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**Core tip:** We sought to determine the prevalence of patients at risk for obstructive sleep apnea (OSA) and the feasibility of screening patients for sleep apnea presenting for a routine colonoscopy to our outpatient endoscopy facility. All patients were screened for OSA with the Berlin questionnaire prior to the procedure. Overall, screening patients for sleep apnea at the time of a colonoscopy offers a unique opportunity not only to screen for colon cancer but also to identify patients at high risk for OSA who should undergo further testing.

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## INTRODUCTION

Obstructive sleep apnea (OSA) is extremely common and affects 2%-4% of the population<sup>[1]</sup>, yet around 92% of females and 82% males with OSA are undiagnosed<sup>[2]</sup>. OSA has been associated with an increased cardiovascular mortality and risk for stroke<sup>[3,4]</sup>, and some studies have shown an increased perioperative morbidity and mortality<sup>[5]</sup>. Various screening tools to identify patients at risk for OSA have been utilized including the Berlin questionnaire, the STOP questionnaire, the ASA checklist, and STOP-BANG<sup>[6,7]</sup>. The Berlin Questionnaire has been determined to be one of the best methods for identifying patients likely to have OSA, and has been shown to be helpful in surgical patients in detecting patients at high risk of OSA<sup>[6]</sup>. In one study, patients in the high risk group on the Berlin questionnaire predicted a respiratory disturbance index of greater than 5 with a sensitivity of 86% and a specificity of 77% with a positive predictive value of 89%<sup>[8]</sup>. One study showed that of patients who snored greater than 10 s during their

screening colonoscopies, all were noted to have OSA<sup>[9]</sup>. We sought to determine the prevalence of patients at risk for OSA and the feasibility of screening patients for sleep apnea presenting for a routine colonoscopy to our outpatient endoscopy facility.

## MATERIALS AND METHODS

Adult patients having a colonoscopy only for routine indications at the East Carolina University Outpatient Endoscopy Center between the dates November 3, 2014 and February 12, 2015 were eligible to participate in the study if they did not carry a diagnosis of sleep apnea and had not had a prior sleep study. The study was approved by the East Carolina University and Vidant Medical Center Institutional Review Board. Written informed consent was obtained from all the patients. Enrollment was limited to days with additional personnel present to help enroll patients. Exclusion criteria included our standard exclusion criteria for the outpatient endoscopy center: BMI > 52, age < 18, home oxygen use, cardiac defibrillator, and ASA class 4 patients.

All patients had a determination of their height, weight, BMI, Mallampati score, neck circumference, and whether they had a history of hypertension. The Mallampati was calculated by both the gastroenterologist and the nurse anesthetist, and a consensus was reached prior to performing the procedure. All patients were administered the Berlin questionnaire prior to the procedure by either the attending or the research fellow. Patients were determined to be high-risk if they met at least 2 of the 3 symptom categories for the Berlin questionnaire. If the patient was negative by category 2 or 3, and if they were not aware whether they snored, they were given an equivocal result. The group determined to have a high likelihood of sleep-disordered breathing based upon a positive result on the Berlin questionnaire were recommended to follow-up with the primary care physician to consider a sleep study per standard medical care.

The colonoscopy was performed under standard monitoring for all patients to include blood pressure and continuous heart rate and oxygen saturation monitoring with 2 L of oxygen per nasal cannula. Nurse anesthetist-administered propofol was used for all cases. Patients were given a bolus of propofol by the nurse anesthetist with additional injections every few minutes titrated to a moderate sedation level. Any drops in oxygen saturation < 92% were noted, and patients were also observed for the presence of snoring for > 10 s.

### Statistics analysis

Data were entered manually, and statistical analysis was performed using SAS Version 9.1 (SAS Institute, Cary, NC). Statistical review was performed by a biomedical statistician. Descriptive statistics were performed using standard methods.  $\chi^2$  test and Fischer's exact test were used to test direct association between drop in oxygen saturation < 92% with the results of the Berlin

Table 1 Patient measurements

	Mean	Std Dev	Minimum	Maximum
Age	55.8	10.8	23.0	72.0
Height (inches)	66.7	4.1	55.0	74.0
Weight (lbs)	189.3	50.4	90.0	335.0
BMI (kg/m <sup>2</sup> )	29.9	7.3	17.0	52.0
Neck circumference (cm)	36.7	4.3	27.0	48.0

BMI: Body mass index.

questionnaire and snoring and with the results of the Berlin questionnaire. A two sample *t*-test was used to test direct association between height, weight, BMI, neck circumference, and the Berlin questionnaire.

## RESULTS

A total of 60 patients were enrolled and completed the study; mean age was 56 (range 23-72 year). The baseline demographics are listed in Table 1. The ASA classification results were as follows: ASA class 1-10 patients (16.7%); ASA class 2-30 patients (50.0%); ASA class 3-20 patients (33.3%). There were no ASA class 4 patients as they were not eligible for our outpatient endoscopy facility.

The indications for the procedures included screening for colon cancer (34 patients), history of colon polyps (10 patients), rectal bleeding (4 patients), inflammatory bowel disease surveillance (3 patients), change in bowel function (2 patients), heme-positive stools (2 patients), diarrhea (2 patients), abdominal pain (2 patients), and a history of colon cancer (1 patient). The baseline Mallampati results can be seen in Table 2.

Twenty-six patients had a positive Berlin questionnaire (43.3%), 31 patients had a negative Berlin questionnaire (51.6%) and 3 patients had an equivocal result (5.0%). The patients with the equivocal Berlin questionnaire results were excluded from the analysis. Nine of the 57 patients had snoring > 10 s (15.8%), and 13 of the 57 patients (22.8%) had a drop in oxygen saturation < 92%.

Patients with a positive Berlin questionnaire were more likely to have an increased neck circumference (38.4 cm vs 35.5 cm,  $P = 0.012$ ), increased weight (mean 210.5 lbs vs mean 169.8 lbs,  $P = 0.003$ ), and have an increased BMI (33.0 kg/m<sup>2</sup> vs 26.8 kg/m<sup>2</sup>,  $P = 0.0016$ ). Patients with snoring were more likely to have a positive Berlin questionnaire (8/9 patients vs 1/31 patients with negative Berlin questionnaire,  $P = 0.0045$ ). Patients with a positive Berlin questionnaire were more likely to have a drop in oxygen saturation < 92% (76.9% vs 36.4%,  $P = 0.01$ ).

## DISCUSSION

In our study, 43% of patients had a positive Berlin questionnaire, and thus were considered to be at high risk for OSA. This demonstrates the reality that many patients with sleep apnea are not being identified, and

Table 2 Mallampati

Mallampati	Frequency	%
1	10	16.67
2	30	50.0
3	18	30.0
4	2	3.3

this underscores the need to develop novel methods to identify patients at risk for OSA. Making screening for OSA routine at the time of a screening colonoscopy would greatly increase the screening of the population for OSA and ensure that a large portion of the population is screened at the age of 50. This is similar to the rationale for screening patients for hepatitis C during the visit for a routine colonoscopy that has been suggested by some<sup>[10]</sup>. Screening patients for OSA with the Berlin questionnaire at the time of the procedure is less labor-intensive than screening for viral hepatitis and involves a simple questionnaire.

Forty-three percent of patients in our study had a positive Berlin questionnaire. This is similar to results observed by Mehta *et al*<sup>[11]</sup> in which 48% had a positive score on the STOP-BANG questionnaire administered at the Cleveland Clinic. In the study by Cote', 43% of patients presenting to a tertiary medical center for endoscopic retrograde cholangiopancreatography or endoscopic ultrasound had a positive score on the STOP-BANG test<sup>[12]</sup> and were more likely to have hypoxemia or require the need for airway maneuvers. Mador *et al*<sup>[13]</sup> also showed that 39% of patients at a Veterans Affairs outpatient endoscopy center identified as high-risk for OSA as defined by the Berlin questionnaire. Our study illustrates that a large portion of patients presenting to our university-based outpatient endoscopy center are likely to have undiagnosed OSA. This agrees with the results of other studies showing that many patients with OSA are not being screened and identified. Screening patients for OSA at the time of their colonoscopy offers a unique opportunity to increase the screening rate for OSA as we also strive to increase the screening rate for colorectal cancer. With rising obesity rates, undiagnosed OSA is likely to increase<sup>[11]</sup>.

Snoring during a colonoscopy has been noted to be a strong predictor of OSA. In the study by Sharara *et al*<sup>[9]</sup> all the patients investigated who snored during conscious sedation for their colonoscopy were diagnosed with OSA, with 70% of these found to have moderate to severe OSA. In our study, patients with snoring > 10 s were more likely to have a positive Berlin questionnaire. Endoscopists should monitor their patients closely for the presence of snoring > 10 s during colonoscopy. If this is noted, these patients should be referred for further sleep testing as there is a very strong likelihood that they have OSA.

We found patients with a positive Berlin questionnaire were more likely to have a drop in oxygen saturation. Some other studies have also noted more oxygen

desaturations in patients with high risk for OSA<sup>[12]</sup>, although Khiani and Mador did not find an increased risk<sup>[13, 14]</sup>. However, in the study by Mehta *et al.*<sup>[11]</sup> patients with undiagnosed sleep apnea undergoing routine upper endoscopy or colonoscopy with propofol sedation were not noted to have an increased risk of "sedation-rated adverse events". Mador *et al.*<sup>[13]</sup> noted a similar finding in that patients with OSA undergoing endoscopic procedures with conscious sedation did not have an increased risk of cardiopulmonary complications.

Endoscopists carefully evaluate the airway of each patient who undergoes sedation for gastrointestinal procedures, including colonoscopy. They are responsible for the sedation of large numbers of patients and offer a select group of physicians with the skill and experience to carefully evaluate patients at risk for OSA. Overall, screening patients for sleep apnea at the time of a colonoscopy offers a unique opportunity not only to screen for colon cancer but also to identify patients at high risk for OSA who should undergo further testing.

## ACKNOWLEDGMENTS

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## COMMENTS

### Background

Obstructive sleep apnea (OSA) is extremely common and affects 2%-4% of the population, yet many patients with OSA are undiagnosed or never undergo screening for OSA.

### Research frontiers

Sharara *et al* noted that of patients who snored greater than 10 s during their screening colonoscopies, all were noted to have OSA. The authors sought to determine the prevalence of OSA and the feasibility of screening these patients with the Berlin questionnaire at the time of their routine colonoscopy.

### Innovations and breakthroughs

Endoscopists carefully evaluate the airway of each patient who undergoes sedation for gastrointestinal procedures, including colonoscopy. Screening patients for sleep apnea at the time of a colonoscopy offers a unique opportunity not only to screen for colon cancer but also to identify patients at high risk for OSA who should undergo further testing and adds little overall time to the procedure.

### Applications

Screening patients for sleep apnea at the time of a screening colonoscopy is not only feasible but adds little time to the overall procedure, and offers a unique opportunity to screen patients for OSA that otherwise may never be screened.

### Peer-review

This is an interesting study of screening for patients for sleep apnoea during colonoscopy. The paper is well written and presents a convincing proposal which may not have been addressed before as it crosses a field not handled

normally by gastroenterologists.

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## Observational Study

## Information seeking and anxiety among colonoscopy-naïve adults: Direct-to-colonoscopy vs traditional consult-first pathways

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**Informed consent statement:** All study participants were informed about the purpose of the study verbally and in writing. Submission of a completed survey constituted informed consent to participate in the study.

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### Abstract

#### AIM

To investigate the effects of direct to colonoscopy pathways on information seeking behaviors and anxiety among colonoscopy-naïve patients.

#### METHODS

Colonoscopy-naïve patients at two tertiary care hospitals completed a survey immediately prior to their scheduled outpatient procedure and before receiving sedation. Survey items included clinical pathway (direct or consult), procedure indication (cancer screening or symptom investigation), telephone and written contact from the physician endoscopist office, information sources, and pre-procedure anxiety. Participants reported pre-procedure anxiety using a 10 point scale anchored by "very relaxed" (1) and "very nervous" (10). At least three months following the procedure, patient medical records were reviewed to determine sedative dose, procedure indications and any adverse events.

The primary comparison was between the direct and consult pathways. Given the very different implications, a secondary analysis considering the patient-reported indication for the procedure (symptoms or screening). Effects of pathway (direct *vs* consult) were compared both within and between the screening and symptom subgroups.

### RESULTS

Of 409 patients who completed the survey, 34% followed a direct pathway. Indications for colonoscopy were similar in each group. The majority of the participants were women (58%), married (61%), and internet users (81%). The most important information source was family physicians (Direct) and specialist physicians (Consult). Use of other information sources, including the internet (20% *vs* 18%) and Direct family and friends (64% *vs* 53%), was similar in the Direct and Consult groups, respectively. Only 31% of the 81% who were internet users accessed internet health information. Most sought fundamental information such as what a colonoscopy is or why it is done. Pre-procedure anxiety did not differ between care pathways. Those undergoing colonoscopy for symptoms reported greater anxiety [mean 5.3, 95%CI: 5.0-5.7 (10 point Likert scale)] than those for screening colonoscopy (4.3, 95%CI: 3.9-4.7).

### CONCLUSION

Procedure indication (cancer screening or symptom investigation) was more closely associated with information seeking behaviors and pre-procedure anxiety than care pathway.

**Key words:** Direct access colonoscopy; Colonoscopy/ utilization; Information seeking behavior; Referral and consultation; Health care delivery; Anxiety

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**Core tip:** Direct access colonoscopy pathways are increasingly common, yet there has been relatively little scrutiny of how this practice impacts patients. This study examines the relationships among endoscopy pathway (direct *vs* traditional consult first), colonoscopy indication (cancer screening *vs* symptom investigation), information seeking behavior and pre-procedure anxiety. Patients undergoing their first colonoscopy completed questionnaires immediately prior to the procedure, before receiving sedation. The finding that direct-to-colonoscopy did not impact patient pre-procedure anxiety is reassuring. Analysis of information seeking behaviors underscores the crucial role of the family physician for referred patients who follow a direct-to-endoscopy pathway.

Silvester JA, Kalkat H, Graff LA, Walker JR, Singh H, Duerksen DR. Information seeking and anxiety among colonoscopy-naïve adults: Direct-to-colonoscopy *vs* traditional consult-first pathways. *World J Gastrointest Endosc* 2016; 8(19): 701-708 Available from: URL: <http://www.wjgnet.com/1948-5190/full/>

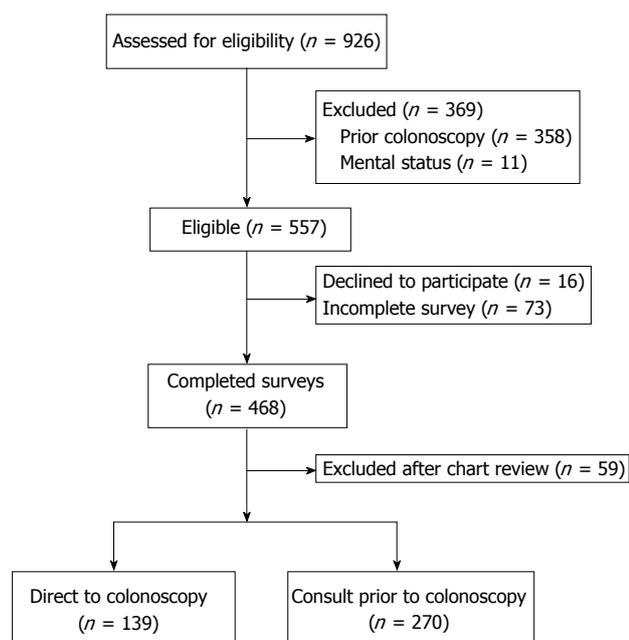
## INTRODUCTION

As demands for prompt diagnostic and therapeutic colonoscopy have increased, direct to colonoscopy pathways have become common in many centers in North America<sup>[1]</sup>. Direct to colonoscopy, also referred to as "open access colonoscopy", allows for provision of a colonoscopy without clinical consultation with the endoscopist prior to the day of the procedure. In an era of lengthy consultation waitlists and limited clinic resources<sup>[2]</sup>, this pathway has potential to facilitate expedited clinical care for many patients. Timely access is critical because delays in diagnostic colonoscopy may result in significant delays in cancer diagnosis<sup>[3,4]</sup>.

Despite being an increasingly common practice associated with appropriate utilization and diagnostic yield<sup>[5-7]</sup>, there is a paucity of data regarding how direct to colonoscopy pathways affect patients. It is essential for the success of the procedure that patients receive adequate information prior to the colonoscopy, including information about bowel preparation, and risks and benefits related to the procedure<sup>[8]</sup>. Studies performed during the 1990s showed that direct to colonoscopy pathways were associated with receiving significantly less of this information prior to the procedure<sup>[9]</sup>. Since then, using the internet to access health information has become a much more common practice<sup>[10]</sup>, and there are many other potential sources of information available to patients in addition to the specialist clinics. It is unknown whether the internet is commonly searched by patients prior to undergoing their first colonoscopy, what information they look for or how they use the information.

Persons undergoing an endoscopic procedure for the first time often experience heightened anxiety<sup>[11]</sup>. It is not known if patients who do not have an opportunity to address issues of concern directly during a specialist consultation experience greater anxiety or if they are more likely to seek information from other sources.

The aims of this naturalistic study were to compare information seeking behavior (including use of the internet), pre-procedure preparation and anxiety level between patients following the direct pathway and patients undergoing colonoscopy after clinical consultation with an endoscopist (consult pathway). We hypothesized that patients who follow a direct to endoscopy pathway are more likely to use the internet to obtain information regarding their procedure and may have heightened pre-procedure anxiety compared to those whose endoscopy referral pathway includes a pre-procedure consultation with the endoscopist. The implications of a colonoscopy for colon cancer screening and a colonoscopy triggered by symptoms are very different; therefore, we performed a secondary analysis considering the patient-reported indication for the procedure (symptoms or screening). An understanding of these factors will help to optimize patient preparation for their procedure and their



**Figure 1 Participant recruitment.** Recruitment and exclusions of patients participating in study.

colonoscopy experience, particularly for those following a direct to colonoscopy pathway.

## MATERIALS AND METHODS

From May 2011 to August 2012, consecutive adults presenting for elective outpatient colonoscopy at the two largest hospitals in Winnipeg, Canada (serving a population of 800000) were invited to complete a pre-endoscopy survey. As this was a naturalistic study, assignment of patients to direct to colonoscopy or pre-procedure consultation was not randomized. Rather, assignment followed the usual practice of the endoscopist reviewing the information provided by the referring physician to determine the appropriate care pathway. This information typically includes patient sex, date of birth and a brief description of the symptoms prompting gastrointestinal consultation. Exclusion criteria were: (1) prior endoscopy; (2) concurrent gastroscopy and colonoscopy; and (3) unable to complete the survey due to language or cognitive difficulties. The study protocol was approved by the Research Ethics Board at the University of Manitoba.

Sample size was estimated assuming a 2:1 allocation to the consult and direct pathways. Assuming a standard deviation of 264 in the Direct group and 128 in the Consult group are needed to detect a 1 point difference in self-reported anxiety with a type I error rate of 5% and power of 80%.

Colonoscopies were performed by a physician endoscopist (gastroenterologist or surgeon). Written information was provided to patients in advance with modest differences in content and detail between clinics. Patient information included: A description of the procedure and use of sedation; a description of the post-procedure

process and follow-up; a list of potential adverse events, and instructions regarding the bowel preparation, diet, and medication use prior to the procedure.

Patients completed the survey after registering and prior to receiving sedation for their colonoscopy. The survey included items related to: (1) demographic characteristics; (2) sources of information about the colonoscopy (written information, internet, friends and family, appointment with endoscopist, telephone contact - yes/no response); (3) ranking of the three most important sources of information about the colonoscopy (10 sources listed); (4) internet use to learn about aspects of the colonoscopy (8 questions, yes/no response); (5) whether they had seen a video of a colonoscopy (yes/no response); and (6) details of type of bowel preparation used, whether they took time off work and if they completed the preparation successfully. Anxiety about the procedure was assessed with the question "how do you feel about your endoscopy today?" using a 10-item numerical rating scale, anchored by (1) very relaxed and (10) very nervous. For analysis, anxiety was characterized as "low" (a rating of 1 to 4), "moderate" (5 to 7) or "high" (8-10). Participants identified whether the colonoscopy was for cancer screening or for symptoms.

Hospital medical records of all participants were reviewed at least 3 mo after the procedure to document procedure-related processes, including indication for the colonoscopy, dose of sedative agents used, findings at colonoscopy and any adverse events.

Data were analyzed using SPSS version 15.0. Patients in the direct to colonoscopy (Direct) pathway were compared with patients who had received a pre-procedure consultation with the endoscopist who subsequently performed the procedure (consult pathway). Means and 95%CI or standard deviation were calculated for all variables as appropriate. The implications of a colonoscopy for colon cancer screening and a colonoscopy triggered by symptoms are very different; therefore, we performed a secondary analysis considering the patient-reported indication for the procedure (symptoms or screening). The effects of pathway (direct vs consult) were compared both within and between the screening and symptom subgroups. The 95%CIs around the estimates (mean or proportions) were used to make comparisons and the differences were considered significant if there was no overlap of 95%CIs or 95%CI around calculated differences did not cross zero.

## RESULTS

Of the 926 patients screened for study participation, 409 fulfilled study criteria and completed the pre-procedure survey (Figure 1). The most common reason for exclusion was prior endoscopy. A further 59 were excluded when chart review identified a previous endoscopy or concurrent gastroscopy. The mean age of participants was 55 years (SD 8.6). The majority of the participants were women (58%), married (61%), and internet users (81%). The demographic characteristics

**Table 1 Background characteristics of patients and colonoscopy processes comparing direct to colonoscopy and pre-procedure consult**

	Direct (n = 139) % (95%CI)	Consult (n = 270) % (95%CI)
Highest level of education		
High school or less	35 (27-43)	37 (31-43)
Trade or non-university certificate	29 (21-37)	35 (29-41)
University	36 (28-44)	28 (23-33)
Marital status - married	60%	62%
Internet user	81%	81%
Used internet to learn about colonoscopy	29%	32%
Patient indication screening	n = 76	n = 117
% of screening high risk	60 (48-72)	49 (40-58)
Patient indication symptoms	n = 63	n = 153
Bloating	86 (77-95)	78 (70-86)
Diarrhea	78 (68-88)	68 (60-76)
Abdominal cramps and/or pain	76 (65-87)	72 (64-80)
Constipation	54 (42-66)	61 (52-70)
Blood in stool	50 (38-62)	37 (28-46)
Nausea or vomiting	35 (23-47)	35 (26-44)
Weight loss	30 (19-41)	36 (27-45)
Pre-procedure information		
Telephone contact	69 (58-80)	48 (39-57)
Written information	94%	96%
Age in years mean (IQR)	56 (54-58)	54 (53-56)
Sex - female	59%	57%

Bolded values indicate pairs for which confidence intervals do not overlap. IQR: Interquartile range.

**Table 2 Most important sources of information for learning about colonoscopy comparing direct to colonoscopy and pre-procedure consult care pathways**

	Most important		Among top three most important	
	Direct % (95%CI)	Consult % (95%CI)	Direct % (95%CI)	Consult % (95%CI)
Any physician	51 (43-59)	69 (63-75)	81 (75-88)	89 (85-93)
Family physician	37 (29-45)	26 (21-31)	59 (51-67)	39 (33-45)
Specialist physician	14 (8-20)	43 (37-49)	22 (15-29)	50 (44-56)
Family and friends	13 (7-19)	10 (6-14)	64 (56-72)	53 (47-59)
Internet	7 (3-11)	4 (2-6)	20 (13-27)	18 (13-23)
Other	3 (0-6)	3 (1-5)	20 (13-27)	13 (9-17)

Bolded values indicate pairs for which CI do not overlap. Note: Participants reviewed 10 potential sources of information and ranked the three most important.

of those in the direct and consult groups were similar (Table 1). Virtually all patients in both groups reported receiving written information about their procedure.

A greater proportion of patients in the Direct group received a pre-procedure telephone call from the physician’s office with relevant pre-procedure preparation information (Direct 69% vs Consult 48%; Table 1). Receiving a pre-procedure telephone call was not associated with pre-procedure anxiety, sedation use, or information-seeking behavior (data not shown).

Ranking of the importance of information sources that were accessed to learn more about colonoscopy is described in Table 2. Both groups identified physicians as the most important source of information. Family and friends were also an important source of information for both groups, with 64% (56%-72%) in the direct group and 53% (47%-59%) in the Consult group rating them among the three most important sources of information.

As expected, those following the direct pathway obtained information from a specialist physician less often, and were more likely to rate information from a family physician among the top three most important information sources [59% (51%-67%) vs 39% (33%-45%)]. The use and importance of other information sources, including the internet, did not differ between the two groups.

The rate of general internet use was 81% in both groups (n = 301), with about 30% reporting they used the internet to learn more about colonoscopy. The pattern of responses shown in Table 3 suggests that among the respondents who used the internet to obtain information about colonoscopy (n = 301), there was interest in a wide range of questions which did not differ between care pathways. Considering the indication for colonoscopy, those referred for symptoms accessed internet health information more often than those in the screening group [48% (40%-56%) vs 28% (20%-36%)]. Despite the

**Table 3 Use of the internet to answer questions about colonoscopy by regular internet users (n = 301) comparing care pathway and indication**

	Care pathway		Indication	
	Direct (n = 104) % (95%CI)	Consult (n = 197) % (95%CI)	Screening (n = 166) % (95%CI)	Symptoms (n = 135) % (95%CI)
What is a colonoscopy	29 (20-38)	32 (26-39)	23 (16-31)	38 (31-46)
How to prepare for colonoscopy	16 (8-23)	24 (17-30)	15 (9-22)	26 (19-33)
What happens during colonoscopy	20 (12-28)	26 (19-32)	17 (10-24)	30 (22-37)
How much time does a colonoscopy take	13 (6-19)	20 (14-26)	14 (8-20)	21 (15-28)
What to expect after colonoscopy	11 (5-18)	18 (12-24)	12 (6-18)	19 (13-26)
Why colonoscopy is done	30 (21-40)	28 (22-35)	19 (12-26)	37 (29-45)
Risks of colonoscopy	19 (11-27)	22 (16-28)	16 (10-23)	25 (18-32)
What is a biopsy	11 (5-18)	14 (9-19)	9 (4-14)	17 (11-23)
Saw video of colonoscopy	24 (15-33)	17 (11-22)	19 (12-25)	20 (13-26)

Bolded values indicate pairs for which confidence interval do not overlap.

**Table 4 Bowel preparation, time off work and sedation used for colonoscopy comparing direct to colonoscopy and pre-procedure consult pathways**

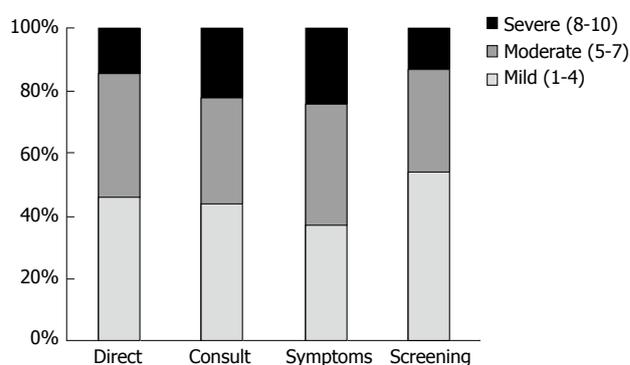
	Direct (n = 139) % (95%CI)	Consult (n = 270) % (95%CI)
Bowel prep		
Picosulfate and magnesium oxide	69 (60-76)	71 (65-77)
Polyethylene glycol	17 (11-24)	14 (10-18)
Other	14 (8-20)	15 (11-19)
Completion of bowel prep	98%	98%
Time off work for bowel prep		
Full-time workers (n = 188)	56 (43-69)	64 (56-72)
Part-time workers (n = 52)	42 (20-64)	50 (29-71)
Sedation		
Midazolam (mg)	5.6 (5.2-5.9)	4.7 (4.5-4.9)
Fentanyl (µg)	106 (100-111)	93 (89-97)

Bolded values indicate pairs for which confidence intervals do not overlap.

wealth of information available on the internet, including well-produced videos, only 1 in 6 patients had seen a video of a colonoscopy prior to the procedure.

There was no difference in the type of bowel preparation used or the self-reported completion of bowel preparation between the two groups (Table 4). Most respondents took time off work to complete bowel preparation, but there was no difference between the Direct and Consult care pathways.

Overall, 20% of participants reported high pre-procedure anxiety. In both care pathways, females reported significantly higher pre-procedure anxiety than males [overall females 5.3 (5.0-5.7), males 4.3 (3.9-4.7); 95%CI for difference 0.76-1.9]. There were no differences in the pre-procedure anxiety levels among individuals in the Direct group compared with the Consult group [mean 4.7 (95%CI: 4.3-5.2) vs 5.0 (95%CI: 4.6-5.3)]. Similarly, there was no statistical differences in proportions reporting low, moderate or high pre-procedure anxiety, comparing the Direct and Consult groups (Figure 2). Mean pre-procedure anxiety was lower among those undergoing screening colonoscopy, but the difference was significant only within the Consult group (males 4.2 vs females 5.4; 95%CI for difference



**Figure 2 Anxiety levels comparing clinical pathway and indication for colonoscopy.** Anxiety levels comparing care pathway and indication for colonoscopy. Anxiety ratings on a 10 point Likert scale were categorized as mild (1-4), moderate (5-7) or high (8-10).

0.5-2.0). There were 311 participants for whom the self-reported indication matched the indication documented in the medical record. In sensitivity analysis, the relationship between procedure indication and pre-procedure anxiety was observed among this group for both care pathways (Direct 4.4 vs 5.4; Consult 4.1 vs 5.5). Mean anxiety levels among those for whom the patient-reported and documented indication were discordant were similar to the population mean. In the Direct group, the relationship between pre-procedure anxiety and indication was attenuated (screening 4.2, non-screening 4.6). Among the Consult group, the relationship was reversed, with higher anxiety levels reported by those undergoing screening colonoscopy (5.1 vs 4.8). This difference persisted even when those identified as high-risk were excluded from the analysis (data not shown).

Patients in the Direct group received more midazolam (5.4 mg vs 4.6 mg, 95%CI: 0.41-1.2 mg) and fentanyl (105 µg vs 93 µg; 95%CI: 5-20 µg). This association between direct pathway and midazolam use was also observed within the screening and symptom sub-groups (data not shown). Midazolam and fentanyl doses were unrelated to self-rated pre-procedure anxiety, indication for the procedure or duration of the procedure (data not shown). There were no sedation or procedure related

adverse events reported, based on the chart review.

## DISCUSSION

This observational study clarifies the real-world effects of referral pathway upon the behaviors and experiences of colonoscopy-naïve patients. We hypothesized that those in the direct (open access) pathway would display more information seeking behaviors and may experience more anxiety related to the procedure given that they did not have the benefit of a consultation with the physician endoscopist prior to the day of their procedure. We found that information seeking behaviors and anxiety were more closely associated with the indication for the procedure (colon cancer screening vs for diagnosis of symptoms) than by the referral pathway. This illustrates the intricacy of designing referral pathways to optimize the utilization of scarce clinical and endoscopy resources while providing care which meets the needs of the patient. It also underscores the importance of primary care physicians in the continuum of care.

The pattern of information seeking behavior did not differ between the two care pathways. Even with the plethora of electronic and other resources available, the patient-physician relationship was paramount for obtaining information regarding colonoscopy. Patients following a direct pathway received this information from a primary care physician, while patients in the Consult group received this information from an endoscopist.

This study was conducted in Canada where there is one of the highest rates of internet penetration<sup>[12]</sup> and the majority of the population has used the internet to access health information<sup>[10]</sup>. Over 80% of patients in our study were internet users; however, only 30% of them used the internet to learn more about colonoscopy. Patients who accessed internet health information sought to answer fundamental questions related to what a colonoscopy is and why is it done, with fewer reporting having delved more deeply into details such as biopsy or the risks of colonoscopy. This observation is concerning given a narrative review of the relationships between lower endoscopy and clinical outcomes which concluded that providing written information and reminders improve adherence to procedures, but that a large proportion of patients have poor comprehension of the risks, benefits and alternatives to colonoscopy<sup>[13]</sup>. The general nature of information sought by participants in our study indicates a need for additional educational initiatives to increase patient knowledge about the procedure which encompasses more than instruction for achieving a quality bowel preparation.

The role of the internet in educating patients about colonoscopy prior to their procedure has not been studied. Given that over 80% of patients in this study were internet users, there is opportunity to develop internet resources or more proactively use appropriate existing resources to support physicians in preparing patients for endoscopic procedures. Advantages of the internet

are that it is accessible for most people, can present video materials easily, and allows the user to choose how much material to review, depending on information preferences and previous knowledge. Video materials have the advantage that they can present information vividly and may impart information about the procedure more easily than text-based information. There are currently resources on the internet that provide realistic and positive depictions of the patient experience before and during a colonoscopy<sup>[14,15]</sup>, but they do not appear to be widely used by patients preparing for their first colonoscopy.

We hypothesized that increased pre-procedure anxiety might be an unintended and unrecognized consequence of direct to colonoscopy pathways. However, in our study of colonoscopy-naïve individuals, pre-procedure anxiety was similar regardless of referral pathway. There were a significant minority (20%) who reported high pre-procedure anxiety, with higher anxiety levels reported by women than by men. There is one other report of the relationship between direct to colonoscopy pathway and pre-procedure anxiety<sup>[11]</sup>. That study was also an observational study, but included patients who had previously undergone an endoscopic procedure as well as patients undergoing gastroscopy. Nevertheless, similar to our study, the direct to colonoscopy pathway was not associated with increased pre-procedure anxiety<sup>[11]</sup>. We found, understandably, that participants undergoing colonoscopy for symptom investigation reported greater pre-procedure anxiety than participants whose endoscopy was for colorectal cancer screening. Among the entire group, the majority of participants reported moderate or high anxiety related to their procedure, irrespective of the pathway or indication.

Clearly, allaying pre-procedure anxiety may be helpful in optimizing the experience of patients undergoing a colonoscopy, yet there have been few studies which have evaluated interventions to decrease pre-procedure anxiety<sup>[16-18]</sup>. For colonoscopy-naïve patients, education has been found to effectively decrease anxiety when delivered either as a ten minutes video at the pre-procedure visit<sup>[17]</sup> or as a detailed information pamphlet about colonoscopy<sup>[19]</sup> in addition to standard written information. Provision of written instruction and information was associated with decreased pre-procedure anxiety in a cohort of patients who had undergone a previous endoscopic procedure<sup>[18]</sup>.

The content of the information provided is also relevant to pre-procedure anxiety. Provision of a colonoscopy pamphlet developed by the American Gastroenterology Association which explained all aspects of colonoscopy and why it is done in addition to "standard colonoscopy preparation instructions" (which focused primarily on the details of the bowel prep) may decrease pre-procedure anxiety<sup>[19]</sup>. Interestingly, in a randomized study in which participants were invited to watch an informational video in addition to receiving standard information, offering the choice did not result in a reduction in pre-procedure anxiety, yet all patients who viewed the video

experienced less pre-procedure anxiety<sup>[17]</sup>.

An unexpected finding of our study was that patients following the direct pathway received higher doses of sedative medications than patients who had a pre-procedure consult. This was not significantly associated with self-reported pre-procedure anxiety, indication for the procedure, or duration of the procedure. While the lack of association between pre-procedure anxiety and sedation requirements during colonoscopy has been reported<sup>[20]</sup>, referral pathway has not previously been identified as a risk factor for increased sedation requirement. The relationship between referral pathway and sedation use during colonoscopy merits further study, not only to improve our limited understanding of the complex factors contributing to sedation requirements<sup>[21-23]</sup>, but also to determine whether inclusion of this variable would enhance clinical scoring systems to prospectively identify patients with high sedation requirements<sup>[23]</sup>.

A potential consequence of direct to colonoscopy is inadequate instruction regarding the bowel preparation required for the procedure. Adequacy of bowel preparation is considered a quality indicator in colonoscopy<sup>[24]</sup> and is particularly relevant for screening for colorectal cancer, the most common indication for colonoscopy in our patient sample, and in most endoscopy units. Self-reported successful completion of bowel preparation was similar in both care pathways. The quality of bowel preparation was not evaluated because this was not systematically recorded by the endoscopists. The work of other investigators suggests that open access does not compromise the bowel preparation with up to 96% of patients achieving adequate bowel preparation using a split-dose regimen<sup>[25]</sup>.

The primary strength of this study is the use of a naturalistic design to explore a topic about which relatively little is known. This provides insight into patient experiences and behaviors in a real-world scenario reflective of clinical practice.

The use of an observational design is also a limitation. There were multiple endoscopists involved who used several similar, non-identical, pre-procedure information pamphlets. Assignment to the direct to endoscopy pathway was a decision made by the endoscopist without reference to pre-determined standardized criteria or as part of a randomized study design. This may have introduced bias into the study; however, it reflects clinical practice and the distribution of patients between the two pathways was similar at the two study sites. Although the difference was relatively small (11%), there were more patients undergoing screening in the Direct to colonoscopy group compared to the Consult group. This is not unexpected given that age is indicated on the referral and is an indication for screening colonoscopy. Nevertheless, there were no major differences in the demographic characteristics of the two patient groups and the relative differences in pre-procedure anxiety and information seeking behaviors between those who were undergoing colonoscopy for unexplained symptoms and those who were undergoing screening colonoscopy were

similar in both care pathways.

In conclusion, our findings demonstrate that the ramifications of open access colonoscopy encompass far more than improved efficiency and cost savings. Patients in the direct pathway relied upon their family doctor to obtain information about their procedure. In an era of open access colonoscopy, it may be especially important that primary care physicians can provide accurate and relevant information regarding colonoscopy to their patients. This includes specifics about the procedure, the preparation, the risks and the rationale for its use, which is the information that patients were most likely to seek using the internet. Preparation for endoscopy is a complex and multifactorial process which involves more than ensuring an adequate bowel preparation. The value of primary care counseling is underscored by a study in which those who received primary care counseling had greater participation in a colon cancer screening program and required less sedation during their procedure<sup>[26]</sup>.

Colonoscopy-naïve patients who were assigned to a direct to colonoscopy pathway demonstrated similar information seeking behavior, use of the internet as an information source, completion of the bowel prep and levels of pre-procedure anxiety as those who had a pre-procedure outpatient consultation. However, there was a relevant minority of patients with high pre-procedure anxiety which was higher in women and in individuals undergoing a colonoscopy for symptom investigation. Future studies should address ways of optimizing preparation of patients for the colonoscopy and reducing pre-procedure anxiety.

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## COMMENTS

### Background

Direct access colonoscopy pathways are increasingly common as health care systems strive to expedite care and control costs. This is associated with appropriate use and diagnostic yield, but other impacts have not been well-described.

### Research frontiers

This study of colonoscopy-naïve patients investigates information use and anxiety in patients undergoing direct access colonoscopy and compares this with patients who have an initial consult prior to their colonoscopy procedure.

### Innovations and breakthroughs

Open access colonoscopy has ramifications beyond efficiency gains and cost savings. Physicians play a key role in informing patients about colonoscopy and primary care physicians play an especially important role in an open access pathway. Pre-procedure anxiety is more closely associated with patient reported indication for the procedure than with referral pathway.

### Applications

This study supports the practice of direct access colonoscopy. Patients

undergoing direct access colonoscopy do not have increased anxiety and access information about their procedure similar to patients having a specialist consult prior to the procedure. Referral pathways must be responsive to the needs of patients and attentive to the role of referring clinicians to ensure adequately informed and prepared patients.

**Peer-review**

This is an interesting study looking at difference in anxiety between open access and consult first pathways to colonoscopy. The research is well-designed and the overall structure of the manuscript is complete.

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## Prospective Study

**Post-endoscopic retrograde cholangiopancreatography  
pancreatitis: Risk factors and predictors of severity**

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**Institutional review board statement:** This study was approved by the institutional review board of Mansoura University.

**Informed consent statement:** All patients underwent ERCP after a careful explanation of the nature of the disease and possible complications.

**Conflict-of-interest statement:** There are no potential conflicts of interest relevant to this article.

**Data sharing statement:** No additional data are available.

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**Abstract****AIM**

To detect risk factors for post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) and investigate the predictors of its severity.

**METHODS**

This is a prospective cohort study of all patients who underwent ERCP. Pre-ERCP data, intraoperative data, and post-ERCP data were collected.

**RESULTS**

The study population consisted of 996 patients. Their mean age at presentation was 58.42 ( $\pm$  14.72) years, and there were 454 male and 442 female patients. Overall, PEP occurred in 102 (10.2%) patients of the study population; eighty (78.4%) cases were of mild to moderate degree, while severe pancreatitis occurred in 22 (21.6%) patients. No hospital mortality was reported for any of PEP patients during the study duration. Age less than 35 years ( $P = 0.001$ , OR = 0.035), narrower common bile duct (CBD) diameter ( $P = 0.0001$ ) and increased number of pancreatic cannulations ( $P = 0.0001$ ) were independent risk factors for the occurrence of PEP.

**CONCLUSION**

PEP is the most frequent and devastating complication after ERCP. Age less than 35 years, narrower median CBD diameter and increased number of pancreatic

cannulations are independent risk factors for the occurrence of PEP. Patients with these risk factors are candidates for prophylactic and preventive measures against PEP.

**Key words:** Pancreatitis; Obstructive jaundice; Endoscopic retrograde cholangiopancreatography

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**Core tip:** Endoscopic retrograde cholangiopancreatography (ERCP) is increasingly used for therapeutic management of various biliary and pancreatic diseases. However, ERCP is not a procedure without morbidities. Post-ERCP pancreatitis (PEP) remains the most devastating and frequent complication after ERCP. Identification of risk factors for PEP helps adopt prophylactic measures in high risk patients and early discharge in low risk patients. Age less than 35 years, narrower median common bile duct diameter and increased number of pancreatic cannulations were identified to be independent risk factors for the occurrence of PEP.

El Nakeeb A, El Hanafy E, Salah T, Atef E, Hamed H, Sultan AM, Hamdy E, Said M, El Geidie AA, Kandil T, El Shobari M, El Ebdy G. Post-endoscopic retrograde cholangiopancreatography pancreatitis: Risk factors and predictors of severity. *World J Gastrointest Endosc* 2016; 8(19): 709-715 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i19/709.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i19.709>

## INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is increasingly used for therapeutic management of various biliary and pancreatic diseases<sup>[1]</sup>. However, ERCP is not a procedure without morbidities<sup>[2]</sup>. Post-ERCP pancreatitis (PEP) remains the most common and serious complication after ERCP<sup>[3]</sup>. The reported incidence of PEP is around 5%<sup>[4,5]</sup>. This rate may increase up to 20%-40% in high risk patients. Although the majority of PEP cases are of mild degree, it can be severe and life threatening in a substantial proportion of cases<sup>[6]</sup>.

Identification of risk factors for PEP helps adopt prophylactic measures in high risk patients and early discharge in low risk patients<sup>[1,7,8]</sup>. Being convinced with a number of patient-related risk factors, some gastroenterologists and surgeons prefer adoption of alternative management strategies for ERCP whenever possible in high risk patients. Similarly, some endoscopists try to avoid procedure-related risk factors to increase the safety of the procedure. All these factors make identification of risk factors for PEP be of paramount importance for the practice of ERCP.

Many patient and procedure related factors have been suggested to be associated with increased likelihood of PEP<sup>[8]</sup>. The trigger mechanism and pathogenesis for PEP

remain unclear<sup>[9]</sup>. The aim of this study was to detect risk factors for PEP and investigate the predictors of its severity in a tertiary high volume referral surgical center in Middle East in Egypt.

## MATERIALS AND METHODS

This is a prospective cohort study of all patients who underwent ERCP between August 2012 and September 2014. Excluded patients were those who presented with obstructed stent, active pancreatitis, previous endoscopic sphincterotomy, biliary complications after liver transplantation, dye allergy, pregnancy, or mental disability.

Patients were admitted 24 h before the procedure. Baseline laboratory assessment of liver functions, blood count and serum amylase level were done prior to ERCP. No pre-ERCP treatment was used to decrease the risk of PEP. In our center, ERCP is performed under general anesthesia with endotracheal intubation in left semi prone position with monitoring of oxygen saturation, heart rate, and blood pressure. The procedure was performed by experienced endoscopists who had performed at least 1500 ERCPs over the last 10 years. Selective bile duct cannulation was carried out in all patients, but pancreatic duct cannulation was performed when necessary. When three or more attempts were needed due to difficulty in cannulation, precut papillotomy was selectively performed. In addition, endoscopic papillotomy for stone extraction using balloon, basket and mechanical lithotripsy, bile duct placement of either plastic or self-expanding metallic stent, as well as brush cytology and dilation, were performed when indicated. Pancreatic duct stenting was not used to minimize PEP in our practice.

ERCP data were recorded in a standardized manner including all potential risk factors for PEP. Patients were hospitalized for 24 h after the procedure and observed for symptoms and signs of post-ERCP complications. Complete blood picture and serum amylase level were determined routinely after 6 h and 24 h.

PEP was defined and classified according to the consensus definition and grading system<sup>[10]</sup>. PEP was defined as new or worsened abdominal pain together with a serum amylase level at least three times normal at more than 24 h after ERCP and necessitating hospitalization for more than one night. PEP was graded according to the length of hospital stay and the need for intervention. Mild PEP required hospitalization for 2-3 nights, moderate PEP required hospitalization for 4-10 nights, and severe pancreatitis required hospitalization for more than 10 d, or required intervention or was complicated by pseudocyst<sup>[10]</sup>.

Descriptive data are presented as means and standard deviation or medians with range according to the data distribution. Comparison of means was done by  $\chi^2$  test for categorical data or Student's *t* test for continuous data. Difference was considered significant when a *P*-value was less than 0.05. Independent risk factors for PEP were assessed by multiple logistic

**Table 1 Risk factors for pancreatitis after endoscopic retrograde cholangiopancreatography *n* (%)**

	No pancreatitis 894 (89.9)	Pancreatitis 102 (10.2)	<i>P</i> -value
Patient related factors			
Median age (yr)	60	48	0.0001
Age group			
< 35	32 (7.2)	20 (39.2)	0.0001
> 35	415 (92.8)	31 (60.8)	
Sex			
Male	510 (57)	44 (43.1)	0.05
Female	384 (43)	58 (56.9)	
Median serum bilirubin (mg%)	10.6	12.5	0.76
< 2	124 (88.6)	16 (11.4)	
> 2	770 (90)	86 (10)	0.72
Median CBD diameter (mm)	16	10	0.0001
< 10	70 (7.8)	58 (56.9)	
> 10	824 (92.2)	44 (43.1)	0.0001
Indication for ERCP			
Malignant	402 (45)	40 (39.2)	0.43
Benign	492 (55)	62 (60.8)	
Type of papilla			
Normal	540 (60.4)	56 (54.9)	0.01
Atrophic	18 (2)	8 (7.8)	
Pregnant	68 (7.6)	2 (2)	
Tumour	64 (7.2)	4 (3.9)	
Redundant	66(7.4)	12 (11.8)	
Juxtadiverticular	68 (7.6)	16 (15.7)	
Small	60 (6.6)	2 (2)	
Long	10 (1.1)	2 (2)	
Procedure related factors			
Number of cannulation attempts			
< 5	660 (73.9)	58 (56.9)	0.01
≥ 6	234 (26.1)	44 (43.1)	
Number of pancreatic cannulations			
< 3 times	864 (96.6)	60 (58.8)	0.0001
> 3 times	28 (3.4)	42 (41.2)	
Method of cannulation			
Conventional	640 (89.4)	76 (10.6)	0.7
Precut	252 (90.6)	26 (9.4)	
Biliary sphincter balloon dilatation			
No	654 (73.2)	86 (84.3)	0.08
Yes	240 (26.8)	16 (15.7)	

CBD: Common bile duct; ERCP: Endoscopic retrograde cholangiopancreatography

regression. Statistical analyses of the data in this study were performed using SPSS software, version 17 (Chicago, IL).

## RESULTS

From August 2012 to September 2014, a total of 1296 patients underwent ERCP at Gastrointestinal Surgical Center, Mansoura University, Egypt. The study population consisted of 996 cases after exclusion of those who presented with obstructed stent ( $n = 66$ ), active pancreatitis ( $n = 24$ ), previous endoscopic sphinterotomy ( $n = 110$ ), biliary complications after liver transplantation ( $n = 36$ ), dye allergy ( $n = 10$ ), pregnancy ( $n = 14$ ), or mental disability ( $n = 10$ ).

Indications for ERCP were malignant obstructive

jaundice due to periampullary tumor ( $n = 460$ , 46.2%) or hilar cholangiocarcinoma ( $n = 2$ , 0.2%), calcular obstructive jaundice ( $n = 512$ , 51.4%), benign biliary stricture ( $n = 10$ , 1.0%), and post-cholecystectomy biliary leakage ( $n = 12$ , 1.2%). The mean age at presentation was 58.42 ( $\pm 14.727$ ) years. There were 554 male in comparison to 442 female patients, with a male to female ratio of 1.3:1.

Overall, PEP occurred in 102 (10.2%) patients of the study population. Eighty (78.4%) cases were of mild to moderate degree, while severe pancreatitis occurred in 22 (21.6%) patients. The median length of hospital stay in patients with pancreatitis was 3 d (range, 2-15 d). No hospital mortality was reported for any of PEP patients during the study duration. Univariate analysis showed that patient age and narrower CBD diameter are statistically significant patient-related risk factors associated with occurrence and severity of PEP, while increased number of cannulation attempts and pancreatic cannulation more than three times were significant procedure-related risk factors associated with occurrence and severity of PEP. Indication for ERCP was not significantly associated with occurrence of pancreatitis ( $P = 0.4$ ), but it was significantly associated with the severity of PEP ( $P = 0.009$ ) (Tables 1 and 2).

Multivariate analysis after binary logistic regression analysis revealed that patient age less than 35 years ( $P = 0.001$ , OR = 0.035), narrower median CBD diameter ( $P = 0.0001$ ) and increased number of pancreatic cannulations ( $P = 0.0001$ ) were independent risk factors for the occurrence of PEP (Table 3).

## DISCUSSION

PEP is the most common and serious complication after ERCP<sup>[8]</sup>. PEP is associated with higher morbidity and mortality beside its effect in increasing the consumption of hospital resources<sup>[11]</sup>. Identification of clinical and procedural correlates for PEP is of crucial importance in the practice of ERCP. It affects the medical decision regarding patient choice, adoption of pharmacological prophylactic measures, avoidance of procedural risk factors, and determination of the time of discharge after the procedure<sup>[1,7,8]</sup>. Risk factors for PEP have been a matter of controversy and the pathogenesis of PEP is not fully understood yet<sup>[9,11]</sup>. This study reports risk factors for PEP according to the experience of a tertiary high volume surgical center in Egypt.

Despite advanced accessories and novel techniques in ERCP, complication rate after ERCP remained unchanged over the last decade<sup>[7,12]</sup>. According to previous reports, the incidence of PEP ranges from 5% to 40%. This great discrepancy in the reported rates can be attributed to heterogeneity of the definition of PEP and its grading system, variability in data collection, inclusion of diagnostic ERCP in the study, and difference in expertise among endoscopists<sup>[13]</sup>. The incidence of PEP in this cohort was 10.2% with adoption of the consensus definition of PEP<sup>[10]</sup>. Mild to moderate PEP occurred in 80

**Table 2 Predictors of severity of pancreatitis after endoscopic retrograde cholangiopancreatography *n* (%)**

	Mild to moderate pancreatitis (80)	Severe pancreatitis (22)	P-value
Patient related factors			
Median age (yr)	52	30	0.0001
Age			
< 35	26 (32.5)	14 (63.6)	0.0001
> 35	54 (67.5)	8 (36.4)	
Sex			
Male	38 (47.5)	6 (27.3)	0.08
Female	42 (52.5)	16 (72.7)	
Median serum bilirubin (mg%)	14.1	9.9	0.3
< 2	8 (50)	8 (50)	
> 2	72 (85.7)	14 (14.3)	0.07
Median CBD diameter (mm)	10	9	0.0001
< 10	42 (52.5)	16 (72.7%)	
> 10	38 (47.5)	6 (27.3%)	0.0001
Indication for ERCP			
Malignant	39 (97.5)	1 (2.5)	0.009
Benign	41 (66.1)	21 (33.9)	
Type of papilla			
Normal	39	17	0.06
Atrophic	6	2	
Pregnant	0	2	
Tumour	4	0	
Redundant	9	3	
Juxtadiverticular	15	1	
Small	2	0	
Long	2	0	
Procedure related factors			
No. of cannulation attempts			
< 5	46 (57.5)	12 (54.5)	0.03
≥ 6	34 (27.5)	10 (45.5)	
Median number of pancreatic cannulations	2	4	0.0001
< 3 times	58 (72.5)	2 (9.1)	0.0001
> 3 times	22 (52.4)	20 (90.9)	
Method of cannulation			
Conventional	58 (72.5)	18 (81.8)	0.07
Precut	22 (52.4)	4 (18.2)	
Biliary sphincter balloon dilatation			
No	70 (87.5)	16 (72.7)	0.1
Yes	10 (12.5)	6 (27.3)	

CBD: Common bile duct; ERCP: Endoscopic retrograde cholangiopancreatography.

**Table 3 Multivariate logistic regression for analysis of pancreatitis after endoscopic retrograde cholangiopancreatography**

Variable	P-value	Odds ratio	95%CI for EXP(B)	
			Lower	Upper
Age group	0.001	0.035	0.005	0.259
Age	0.519	1.012	0.976	1.050
Sex	0.362	0.143	0.075	0.270
CBD diameter below 10 mm	0.609	0.726	0.212	2.481
CBD diameter	0.000	0.612	0.495	0.757
Difficult cannulation	0.207	0.476	0.150	1.506
No. of pancreatic cannulations below 3	0.117	0.219	0.033	1.460
No. of pancreatic cannulations	0.000	5.258	2.665	10.370
Papilla	0.964			

CBD: Common bile duct.

(8%) patients, while severe PEP occurred in 22 (2.2%) patients. These ratios are concordant with data reported by previous studies<sup>[14-16]</sup>.

Among different patient related risk factors, younger age and non-dilated extrahepatic biliary radicals were independent risk factors for PEP on multivariate analysis

in this study. Also, using a cutoff value of 35 years to divide patients into two groups, the rate of PEP was significantly higher in the younger group by univariate analysis. Younger age has been a subject of controversy regarding its association with PEP<sup>[8]</sup>. Many studies reported an insignificant relation between patient age and likelihood of PEP<sup>[2,17]</sup>. However, Freeman *et al.*<sup>[18]</sup> first reported relatively younger age as a predictor of PEP on multivariate analysis. This finding was confirmed by later studies<sup>[5,16,19]</sup>. Higher incidence of PEP in younger age was explained by the aging effect on pancreatic exocrine function, smaller common bile duct diameter and the higher incidence of sphincter of Oddi dysfunction in younger age<sup>[13,16,18]</sup>.

Management of CBD stones in case of non-dilated extrahepatic biliary system represents a surgical challenge<sup>[20]</sup>. Laparoscopic transcholedochal CBD exploration mandates a CBD diameter of at least 6-8 mm<sup>[21-23]</sup>. According to many studies including this one, normal caliber CBD is associated with increased difficulty of the ERCP procedure<sup>[24-26]</sup>. However, most of recent studies reported absence of association between narrower CBD diameter and PEP<sup>[13]</sup>. Laparoscopic management for surgically fit patients with concomitant gall bladder and CBD stones in case of non-dilated CBD through transcystic CBD exploration or laparoendoscopic Rendezvous is better to avoid or minimize the risk of PEP<sup>[21]</sup>. In case of isolated choledocholithiasis or in patients who are unfit for surgery, prophylactic measures against PEP should be adopted.

In this cohort, difficult cannulation, denoted by frequent cannulation attempts and pancreatic cannulation more than three times, was associated with a higher risk of PEP. The effect of pancreatic duct injection with contrast dye on PEP could not be evaluated because we did not use the conventional contrast cannulation method. The effect of precut sphincterotomy on PEP is controversial<sup>[11]</sup>. Some authors advocate that precut sphincterotomy causes papillary oedema which retains pancreatic secretion resulting in PEP<sup>[8,24]</sup>. On the other hand, some authors indicate that precut sphincterotomy is usually preceded by difficult cannulation through the conventional approach and that the later, not the precut sphincterotomy itself, is responsible for the development of PEP<sup>[26]</sup>. This is supported by the finding that precut sphincterotomy was not reported as a risk factor for PEP from endoscopists who adopted precut sphincterotomy as a preferred technique from the start not just a salvage procedure after difficult cannulation through conventional cannulation methods<sup>[27]</sup>. Early precut leads to more successful cannulation rate without more hazard of morbidity after ERCP<sup>[28-33]</sup>.

Risk factors for PEP have a synergetic effect<sup>[8]</sup>. Jeurnink *et al.*<sup>[1]</sup> suggested that development of prognostic models and scoring systems based on various patient and procedure related risk factors will help in defining patients at the highest risk for PEP. According to this cohort, young patients (< 35 years) with narrow CBD (< 10 mm) who had shown evidence of difficult

cannulation (high number of cannulation attempts or pancreatic cannulation more than three times) are candidates for prophylactic and preventive measures against PEP<sup>[28]</sup>.

Despite the improvement of techniques of ERCP in recent years and increased experiences, the incidence of PEP has not decreased. Therefore, studies to determine risky patients and predict severity of PEP are very important to give the risk factors prophylactic agents for prevention of PEP<sup>[34-37]</sup>. Pre-ERCP administration of rectal indometacin reduced the overall occurrence of PEP without increasing risk of bleeding<sup>[34]</sup>. Some studies reported that the combination of a temporary prophylactic pancreatic plastic stent placement and rectal non-steroidal anti-inflammatory drugs is recommended for preventing PEP in high-risk cases<sup>[34-36]</sup>. Somatostatin can reduce the incidence of PEP but has not been routinely administered in most of centers nor recommended by guidelines as a prophylactic measure for PEP<sup>[36,37]</sup>. Patients at high risk of PEP should be also monitored for at least 24 h to avoid occurrence of PEP after early discharge<sup>[1,7]</sup>.

In conclusion, PEP is the most frequent and devastating complication after ERCP. PEP is associated with higher morbidity and mortality beside its effect in increasing the consumption of hospital resources. Age less than 35 years, narrower median CBD diameter and increased number of pancreatic cannulations are independent risk factors for the occurrence of PEP. Patients with these risk factors are candidates for prophylactic and preventive measures against PEP.

## COMMENTS

### Background

Endoscopic retrograde cholangiopancreatography (ERCP) is increasingly used for therapeutic management of various biliary and pancreatic diseases. However, ERCP is not a procedure without morbidities. Post-ERCP pancreatitis (PEP) remains the most common and serious complication after ERCP. The reported incidence of PEP is around 5%. This rate may increase up to 20%-40% in high risk patients. Identification of risk factors for PEP helps adopt prophylactic measures in high risk patients and early discharge in low risk patients.

### Research frontiers

Many studies have tried to identify the risk factors for pancreatitis after ERCP. Many patient and procedure related factors are suggested to be associated with increased likelihood of PEP. The trigger mechanism and pathogenesis for PEP remain unclear.

### Innovations and breakthroughs

ERCP is not a procedure without morbidities. Identification of risk factors for PEP helps adopt prophylactic measures in high risk patients and early discharge in low risk patients.

### Applications

The data in this study suggested risk factors for PEP and investigated the predictors of its severity in a tertiary high volume. Furthermore, this study also provided readers with important information regarding the risk factors for PEP.

### Terminology

PEP remains the most devastating and frequent complication after ERCP. The reported incidence of PEP is around 5%. This rate may increase up to

20%-40% in high risk patients.

### Peer-review

This is an interesting manuscript with a significant number of patients treating an important topic, and the aim of this study was to detect risk factors for PEP and investigate the predictors of its severity in a tertiary high volume referral surgical center in Egypt.

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## Randomized Controlled Trial

**Vonoprazan 20 mg vs lansoprazole 30 mg for endoscopic submucosal dissection-induced gastric ulcers**

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**Author contributions:** Takahashi K designed this study, collected and analyzed the data and drafted the manuscript; Terai S gave final approval of the version to be published; Sato Y revised the manuscript; Kohisa J, Watanabe J, Sato H, Mizuno K and Hashimoto S took part in this study as endoscopic operators or assistants.

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**Clinical trial registration statement:** This study is registered at UMIN clinical Trial Registry. The registration identification number is UMIN000022006.

**Informed consent statement:** All study participants provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** None declared.

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**Abstract****AIM**

To compare the healing effects of vonoprazan and lansoprazole on gastric ulcers induced by endoscopic submucosal dissection (ESD).

**METHODS**

Data were obtained from a total of 26 patients. Fourteen patients were randomized to the vonoprazan group and 12 were randomized to the lansoprazole group. Patients were administered either 20 mg vonoprazan or 30 mg lansoprazole per day after ESD. Endoscopic images just after ESD, on day 8, and on day 28 were used for the evaluation of the shrinking rate of ESD ulcers. The shrinking rates and the incidence of delayed bleeding were compared between the 2 groups.

**RESULTS**

The shrinking rates of ESD ulcers on day 8 [vonoprazan

group: 61.8% (range: 24.0%-91.1%), lansoprazole group: 71.3% (range: 25.2%-88.6%)] and on day 28 [vonoprazan group: 95.3% (range: 76.2%-100%), lansoprazole group: 97.2% (range: 81.1%-99.8%)] were not statistically different between the 2 groups. On day 28, most of the ulcers in both groups healed to more than 90%, whereas 3 of 14 (21.4%) in the vonoprazan group and 1 of 12 (8.3%) in the lansoprazole group had delayed ulcer healing, which was not statistically different ( $P = 0.356$ ). The frequency of delayed bleeding was 0 in the both groups. Taken together, there were no significant differences between the two drug groups.

### CONCLUSION

Our study indicates that vonoprazan is potent for the management of ESD ulcers although lansoprazole is also sufficient and cost-effective.

**Key words:** Lansoprazole; Gastric cancer; Endoscopic submucosal dissection; Potassium-competitive acid blocker; Proton pump inhibitor; Vonoprazan

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**Core tip:** Our study highlights the comparison of two drugs (vonoprazan and lansoprazole) for the treatment of gastric ulcers induced by endoscopic submucosal dissection (ESD). There were no significant differences between the two drugs with regard to ulcer shrinkage and delayed bleeding. Our study indicated vonoprazan was potent for the management of ESD ulcers although lansoprazole was also sufficient and cost-effective.

Takahashi K, Sato Y, Kohisa J, Watanabe J, Sato H, Mizuno K, Hashimoto S, Terai S. Vonoprazan 20 mg vs lansoprazole 30 mg for endoscopic submucosal dissection-induced gastric ulcers. *World J Gastrointest Endosc* 2016; 8(19): 716-722 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v8/i19/716.htm> DOI: <http://dx.doi.org/10.4253/wjge.v8.i19.716>

### INTRODUCTION

Endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) is a significantly less invasive procedure compared with gastrectomy and is a common procedure. The main advantage of ESD is enabling en-bloc resection of the lesion. Consequently, ESD results in precise histopathological assessment and a low local recurrence rate<sup>[1,2]</sup>. Since en-bloc resection of large lesions is possible with ESD, the iatrogenic ulcers tend to be large and the complications of ESD, including bleeding and perforation, are more frequent than those of endoscopic mucosal resection (EMR)<sup>[1]</sup>. Therefore, the management of ESD-induced ulcers is important to prevent adverse events such as delayed bleeding or perforation.

Acid inhibitors such as proton pump inhibitors (PPIs)

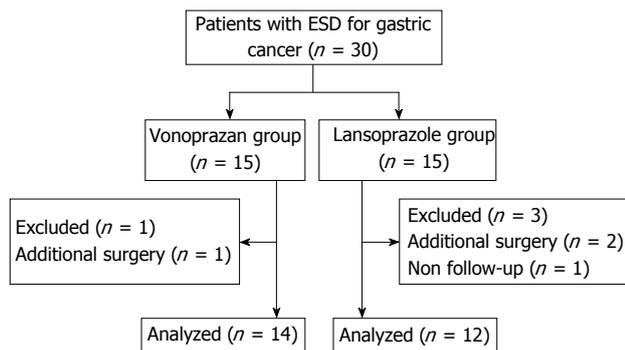
and H<sub>2</sub>-blockers have been used for the treatment of acid related diseases, including ESD-induced ulcers. PPIs are mainly used for the treatment of ESD-induced ulcers owing to their superiority to H<sub>2</sub> blockers<sup>[3,4]</sup>. Although PPIs have been useful for the management of ESD-induced ulcers, they have several limitations including short plasma half-life, slow onset of effectiveness, and the problem of cytochrome P450 (CYP) 2C19 polymorphism<sup>[4-8]</sup>.

The potassium-competitive acid blocker (P-CAB) is a new class of gastric acid suppressant that inhibits gastric H<sup>+</sup>, K<sup>+</sup>-ATPase in a K<sup>+</sup>-competitive and reversible manner<sup>[9,10]</sup>. Vonoprazan was the first orally bioavailable P-CAB and it was approved in Japan in 2014 for the treatment and prevention of acid-related diseases<sup>[11]</sup>. Vonoprazan exhibits rapid, profound, and sustained suppression of gastric acid secretions and is not affected by CYP2C19 polymorphism<sup>[10,12]</sup>. It has been reported that the acid-inhibitory effect of vonoprazan is more potent than that of PPIs<sup>[6]</sup>, resulting in greater effectiveness for acid-related diseases such as gastroesophageal reflux disease (GERD) or *Helicobacter pylori* (*H. pylori*) eradication. Therefore, vonoprazan could be more effective for the management of ESD-induced ulcers compared to PPIs, which are now the gold standard for the management of ESD-induced ulcers. To the best of our knowledge, there have been no reports comparing the healing effect of vonoprazan and PPIs on ESD-induced ulcers. We conducted a prospective randomized controlled study to compare the healing effect of P-CAB (vonoprazan) and PPI (lansoprazole) on ESD-induced ulcers. The primary aim was to evaluate the shrinking rate of ESD-induced ulcers and the secondary aim was to evaluate the preventive effect of vonoprazan on delayed bleeding.

### MATERIALS AND METHODS

#### Patients

Thirty consecutive patients, who underwent ESD for EGC between August 2015 and March 2016 at Sado General Hospital, were enrolled in this study. Their medical records were checked to verify whether they were administered antiplatelet agents, anticoagulants, and steroids. *H. pylori* infection status was confirmed by urease test, histopathology, serum antibody, stool antigen, or urinary antibody. The existence of atrophic gastritis was investigated with the endoscopic images at ESD and classified as closed or open type according to the Kimura-Takemoto classification<sup>[13]</sup>. Before ESD, a chest and abdominal computed tomography scan was performed on all patients. If metastasis or advanced cancer in other organs was detected, the patient was not included in this study. Furthermore, patients who had undergone gastric surgery before ESD were not included in this study. Those who needed any additional anticancer therapy (surgery and/or chemotherapy) after ESD were excluded. Written informed consent was obtained from the patients before enrollment. The study protocol was



**Figure 1** Flow chart of the participants in the study. Thirty patients were enrolled and four of them were excluded because they needed additional surgery or violated the protocol. Finally, 14 patients in the vonoprazan group and 12 patients in the lansoprazole group were included in the analysis. ESD: Endoscopic submucosal dissection.

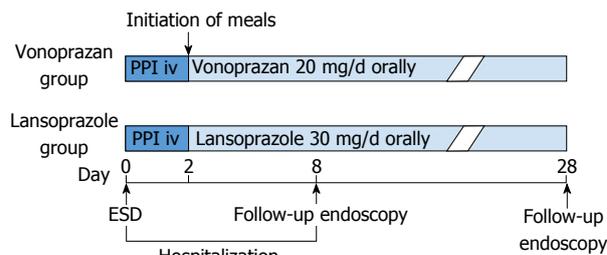
approved by the Sado General Hospital Institutional Ethics Committee and carried out in accordance with the Declaration of Helsinki. This study was enlisted in UMIN clinical Trials Registry (UMIN000022006).

**Study protocol**

Patients were prospectively and randomly assigned into either the vonoprazan or the lansoprazole group using permuted block randomization (Figure 1). The treatment protocol is shown in Figure 2. Patients were admitted a day before ESD. From the day of ESD, intravenous infusion of PPI (lansoprazole 30 mg) was administered to all patients for 2 d. Two days after ESD, oral intake was initiated and patients in the vonoprazan group were administered vonoprazan (20 mg/d) and patients in the lansoprazole group were administered lansoprazole (30 mg/d) until 28 d after ESD. If the patients were already being administered antiplatelet agents or anticoagulants, these medicines were stopped before ESD and resumed 2 d after ESD. Eight days after the ESD, all patients underwent esophagogastroduodenoscopy (EGD) to evaluate the shrinking rate of ESD ulcers. After EGD on day 8, patients were discharged. Twenty-eight days after ESD, patients underwent follow-up EGD and the shrinking rate of the ulcers on day 28 was evaluated.

**ESD procedure**

ESD procedures were performed using a single channel upper gastrointestinal endoscope (GIF Q260J; Olympus, Tokyo, Japan) with a HookKnife (Olympus, Tokyo, Japan) and a DualKnife (Olympus, Tokyo, Japan). An electrosurgical current was applied using a standard electrosurgical generator (ICC 200; ERBE, Tübingen, Germany). The margin of the lesion was circumferentially dotted using a DualKnife in the forced coagulation mode (30 W). After the application of a 10% glycerin solution containing 0.005 mg/mL of epinephrine into the submucosal layer, a mucosal incision was made using a DualKnife in the endo-cut mode (60 W). Then, the submucosal layer was dissected with a HookKnife in the forced coagulation mode (60 W). Hemostatic forceps (Coagrasper; Olympus, Tokyo, Japan) were used to stop



**Figure 2** From the day of endoscopic submucosal dissection, intravenous infusion of proton pump inhibitor (lansoprazole 30 mg) was administered to all patients for 2 d. Then, oral intake was initiated and patients in the vonoprazan group were administered vonoprazan (20 mg daily) and patients in the lansoprazole group were administered lansoprazole (30 mg daily) until 28 d after ESD. Patients underwent follow-up EGD on day 8 and day 28. ESD: Endoscopic submucosal dissection; PPI: Proton pump inhibitor; iv: Intravenous injection.

or prevent bleeding in the soft coagulation mode (80 W).

**Evaluation of ESD results**

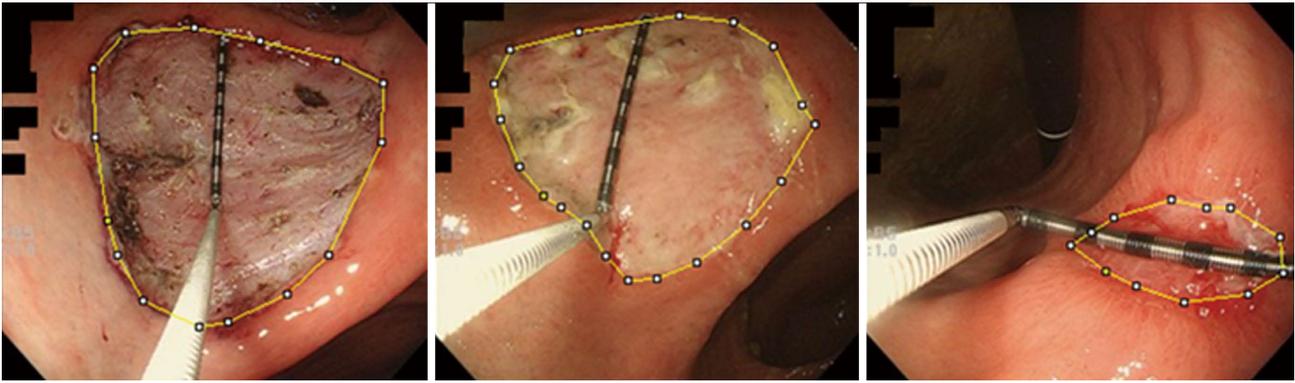
En bloc resection rate, location of the tumors, procedure time, submucosal fibrosis, and histopathology of the tumor were investigated and compared between the two groups. Furthermore, we evaluated the area of ESD ulcer as follows: Endoscopic images were taken just after ESD, on day 8, and on day 28, and image processing software (ImageJ) was used to calculate the area of ESD ulcers (Figure 3). Since this software calculated the area as pixels, measuring forceps were put on the ulcer base and used for the scale, and the area of ESD-induced ulcers was expressed in cubic millimeter. The shrinking rate on day 8 was defined as  $[1 - (\text{the area of ESD-induced ulcer on day 8}) / (\text{the area of ESD-induced ulcer just after ESD})] \times 100 (\%)$  and the shrinking rate on day 28 was defined as  $[1 - (\text{the area of ESD-induced ulcer on day 28}) / (\text{the area of ESD-induced ulcer just after ESD})] \times 100 (\%)$ . Delayed ulcer healing was declared when the shrinking rate on day 28 was less than 90%. The shrinking rates on days 8 and 28 and the frequency of delayed ulcer healing were compared between the 2 groups. The frequency of delayed bleeding was also investigated and compared between the two groups.

**Statistical analysis**

Parametric data are expressed as mean  $\pm$  SD and non-parametric data are expressed as median (range). The  $\chi^2$  test was used for the categorical data and the Student's *t*-test and the Mann-Whitney *U* test were used for the numerical data. SPSS statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, United States) was used for the statistical analyses. *P* values of less than 0.05 were considered statistically significant in the  $\chi^2$  test and the Student's *t*-test. Since the critical value of *U* at *P* < 0.05 in this study was 45, *U* values of less than 45 were considered statistically significant in the Mann-Whitney *U* test.

**RESULTS**

Thirty patients were enrolled and four of them were



**Figure 3** A representative case in the lansoprazole group. The area inside the yellow line was calculated using ImageJ. We placed measuring forceps on the ulcer base to use as a scale. The ulcer base gradually shrank and there were no adverse events. The shrinking rates on days 8 and 28 were 27.1% and 96.3%, respectively.

**Table 1** Backgrounds of the patients and endoscopic submucosal dissection results *n* (%)

	Vonoprazan ( <i>n</i> = 14)	Lansoprazole ( <i>n</i> = 12)	<i>P</i> value
Backgrounds			
Age (yr)	71.9 ± 7.9	74.8 ± 8.3	0.371
Sex (M/F)	12/2	10/2	0.867
Anticoagulants	1 (7.1)	1 (8.3)	0.910
Antiplatelet agents	3 (21.4)	3 (21.4)	0.829
Steroids	1 (7.1)	0 (0)	0.345
<i>Helicobacter pylori</i> infection	4 (28.6)	5 (41.7)	0.484
Atrophic gastritis			
Closed type	3 (21.4)	0 (0)	0.088
Open type	11 (78.6)	12 (100.0)	
Location			
Upper	1	0	0.618
Middle	5	4	
Lower	8	8	
ESD results			
<i>En bloc</i> resection	14 (100.0)	12 (100.0)	
Procedure time (min)	88 (36-246)	51.5 (12-202)	0.123
Submucosal fibrosis	3 (25.0)	1 (8.3)	0.356
Histopathology			
Tub1	12	10	0.504
Tub1 + tub2	1	2	
Tub1 + tub2 + por2	1	0	

Data were expressed as number (%), mean ± SD, or median (range). A *P* value less than 0.05 was considered significant. M: Male; F: Female; ESD: Endoscopic submucosal dissection.

excluded because they needed additional surgery or violated the protocol (Figure 1). Data were obtained from a total of 26 patients. Fourteen patients were randomized to the vonoprazan group and the remaining 12 patients were randomized to the lansoprazole group. There were no statistically significant differences between the two groups with regard to backgrounds, including age and sex; use of anticoagulants, antiplatelet agents, and steroids; *H. pylori* infection state; the degree of endoscopic gastric atrophy; and the location of the tumors (Table 1). Regarding ESD results, *en bloc* resection rate, procedure time, histopathology of lesions, and the frequency of submucosal fibrosis were not statistically different between the two groups (Table 1).

The results of the evaluation of ESD-induced ulcers and delayed bleeding are shown in Table 2. The median areas of ESD-induced ulcers just after ESD in the vonoprazan group and the lansoprazole group were 1446.9 (range: 605-3977.4) mm<sup>3</sup> and 1262.6 (range: 597.8-7322.3) mm<sup>3</sup>, respectively, and were not statistically different. The median shrinking rates of ESD-induced ulcers on day 8 were 61.8% (range: 24.0%-91.1%) in the vonoprazan group and 71.3% (range: 25.2%-88.6%) in the lansoprazole group and those on day 28 were 95.3% (range: 76.2%-100%) in the vonoprazan group and 97.2% (range: 81.1%-99.8%) in the lansoprazole group. The median shrinking rates of ESD-induced ulcers on both days 8 and 28 were not statistically different. On day 28, most of the ulcers in both groups healed to more than 90%, whereas 3 of 14 (21.4%) in the vonoprazan group and 1 of 12 (8.3%) in the lansoprazole group had delayed ulcer healing, which was not statistically different (*P* = 0.356). The frequency of delayed bleeding was 0 in the both groups. Taken together, there were no significant differences between the two drug groups.

## DISCUSSION

In this study, the shrinking rates of ESD ulcers on days 8 and 28 were not statistically different between the two groups, and all of the patients in both groups were discharged without any severe complications. This suggests that lansoprazole was sufficient for the management of ESD ulcers although vonoprazan is theoretically more potent with regard to acid suppression.

PPIs have been widely used for the treatment of acid-related diseases, including ESD ulcers, and the therapeutic effect of PPIs has been satisfactory. However, there are some inadequacies that should be addressed. First, PPIs have a relatively short plasma half-life (60-90 min)<sup>[5,6]</sup>. Therefore, taking PPIs twice a day could be insufficient for inhibiting gastric acid at night. Second, PPIs are prodrugs and are activated under acid-secretion conditions. Hence, the effect of PPIs could be affected by food intake<sup>[4,6]</sup>. Third, since the onset of PPI effect is slow and it takes time to achieve maximum efficacy, rapid effects cannot be achieved<sup>[4,6,7]</sup>. These limitations

**Table 2** The evaluation of the endoscopic submucosal dissection induced ulcers and delayed bleeding

	Vonoprazan	Lansoprazole	<i>P</i> value <sup>1</sup>	<i>U</i> value <sup>2</sup>
Area of the ulcer just after ESD (mm <sup>3</sup> )	1446.9 (605-3977.4)	1262.6 (597.8-7322.3)		89
Results of the follow-up endoscopy				
Area of the ulcer on day 8 (mm <sup>3</sup> )	533.5 (93.6-1735.9)	459.8 (90.5-5479.5)		93
Shrinking rate on day 8 (%)	61.8 (24.0-91.1)	71.3 (25.2-88.6)		70.5
Area of the ulcer on day 28 (mm <sup>3</sup> )	61.6 (0-289.1)	28.7 (1.1-639.4)		93
Shrinking rate on day 28 (%)	95.3 (76.2-100)	97.2 (81.1-99.8)		68
Delayed ulcer healing <i>n</i> (%)	3/14 (21.4)	1/12 (8.3)	0.356	
Delayed bleeding <i>n</i> (%)	0/14 (0)	0/12 (0)	1	

<sup>1</sup> $\chi^2$ ; <sup>2</sup>Mann-Whitney *U* test. Data were expressed as number (%), mean  $\pm$  SD, or median (range). *U* value less than 45 and *P* value less than 0.05 were considered statistically significant. ESD: Endoscopic submucosal dissection.

could affect the clinical course after ESD. Furthermore, the problem of CYP 2C19 polymorphism could also inhibit the effectiveness of PPIs. With regard to CYP2C19 polymorphism, there are inter-ethnic differences regarding the frequency of extensive and poor metabolizers. In the Japanese population, the frequency of poor metabolizers is reported to be 18.0%-22.5%<sup>[8]</sup>. Although the frequency of poor metabolizers is relatively high in Japan compared to that in Western countries, the majority of the population still consists of extensive metabolizers. It has been reported that plasma PPI concentrations and intragastric pH are lower in extensive metabolizers compared with those in poor metabolizers, resulting in poor results of acid-suppression therapies in patients with GERD or *H. pylori* eradication<sup>[4,8]</sup>. Therefore, PPIs could be insufficient for the management of ESD ulcers, especially in extensive metabolizers.

On the other hand, vonoprazan, which is a novel acid inhibitor and classified as a P-CAB, has a long-lasting and rapid effect on gastric acid inhibition, and it is not affected by the acid secretory state, mealtime, or CYP2C19 polymorphism<sup>[5,6,11,12,14]</sup>. It has been reported that vonoprazan is more potent regarding acid inhibition and more efficient for acid-related diseases<sup>[6,11,14]</sup>. Vonoprazan could theoretically be more potent for the management of ESD ulcers. However, in our study, vonoprazan did not show superiority to lansoprazole with regard to ulcer healing after ESD. It has been reported that EMR ulcers heal faster than peptic ulcers because of high blood flow at the margin of EMR ulcers<sup>[15-17]</sup>. The mechanism of ESD ulcers is similar to that of EMR ulcers and even large ESD ulcers heal within 8 wk after treatment with normal doses of PPIs<sup>[18]</sup>. In this study, the area of the ESD ulcers reduced to less than 10% on day 28 in most of the cases in both groups, faster than peptic ulcer healing. Therefore, we concluded that vonoprazan was potent and lansoprazole was also effective for healing ESD ulcers. With regard to medical expenses, vonoprazan (20 mg daily) and lansoprazole (30 mg daily) cost 240 JPY (almost \$2.4) and 140 JPY (almost \$1.4), respectively. In our hospital, we usually use acid suppression medicines for at least 2 mo on the basis of a previous study<sup>[18]</sup>, and the difference in the medical expenses between treatment with vonoprazan and lansoprazole for each patient is up to 5600 JPY (almost \$56). Therefore, lansoprazole is

more cost-effective although both of them are valid for the management of ESD ulcers.

Our secondary aim was the evaluation of the preventive effect of vonoprazan on delayed bleeding compared to lansoprazole. Clinically, the prevention of delayed bleeding is important after ESD, and the frequency of delayed bleeding has been reported to be approximately 5%<sup>[19-24]</sup>. Intragastric pH is an important factor for the coagulation system and platelet aggregation, and the activity of fibrinolysis is impaired at pH values above 6<sup>[25,26]</sup>. The most delayed bleeding occurs within the first 24 to 48 h<sup>[19]</sup>. Therefore, vonoprazan is theoretically superior for the prevention of delayed bleeding owing to its sustained, rapid, and more potent effect on acid suppression<sup>[6,11,12]</sup>. In our study, the delayed bleeding rate was 0% in both groups although our sample size was too small for the precise evaluation of the preventive effect on delayed bleeding. There are several reasons for this result. First, the acid suppression of both vonoprazan and lansoprazole was potent enough to prevent delayed bleeding; second, we carefully coagulated thick blood vessels that might bleed afterward. It has been reported that patients with large lesions or those being administered antithrombotic drugs have a high risk for delayed bleeding or perforation<sup>[19,21-24]</sup>. PPIs are occasionally not adequate to prevent complications in such patients. Vonoprazan is expected to reduce the incident rates of delayed bleeding because of its potent acid suppression.

To the best of our knowledge, this is the first report comparing the healing effects of vonoprazan and lansoprazole on ESD ulcers. However, there are some limitations of this study. First, the sample size was not large enough to obtain conclusive results. However, both vonoprazan and lansoprazole seemed potent enough for the management of ESD ulcers; second, our protocol might not be appropriate because we used intravenous lansoprazole for both groups in the first 2 day after ESD, resulting in underestimation of the healing and preventive effect of vonoprazan; third, we did not investigate the polymorphism of CYP2C19 in this study. This is important for making definitive conclusions. In extensive metabolizers, vonoprazan might prove to be superior to PPIs; fourth, anticoagulant, antiplatelet agent, and steroid users should have been removed from the

study to prevent their associated complications from affecting the comparison. However, they were included in the present study.

In summary, our study indicated vonoprazan was potent for the management of ESD ulcers although lansoprazole was also sufficient and cost-effective. Since vonoprazan theoretically has more potent acid-suppression and is not affected by CYP2C19 polymorphism, it could be more effective in the high risk groups or extensive metabolizers. A further prospective study with these patients is needed to make a definitive conclusion.

## ACKNOWLEDGMENTS

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## COMMENTS

### Background

Proton pump inhibitors (PPIs) have been used for the management of ulcers induced by endoscopic submucosal dissection (ESD). Vonoprazan, an orally bioavailable potassium-competitive acid blocker, is a new class of gastric acid suppressant that inhibits gastric H<sup>+</sup>, K<sup>+</sup>-ATPase in a K<sup>+</sup>-competitive and reversible manner. It was approved in Japan in 2014 for the treatment and prevention of acid-related diseases including ESD-induced ulcers. The aim of this study was to compare the healing effects of vonoprazan and lansoprazole on ESD-induced ulcers.

### Research frontiers

Vonoprazan exhibits rapid, profound, and sustained suppression of gastric acid secretions and is not affected by CYP2C19 polymorphism. It has been reported that the acid-inhibitory effect of vonoprazan is more potent than that of PPIs, resulting in greater effectiveness for acid-related diseases such as gastroesophageal reflux disease or *Helicobacter pylori* eradication. Therefore, vonoprazan could be more effective for the management of ESD-induced ulcers compared to PPIs. So far there have been no reports comparing the healing effect of vonoprazan and PPIs on ESD-induced ulcers.

### Innovations and breakthroughs

The authors compared shrinking rates of ESD-induced ulcers on days 8 and 28 between the vonoprazan group and the lansoprazole group, and showed that the shrinking rates of ESD ulcers on days 8 and 28 were not statistically different between the two groups.

### Applications

The result of this study suggested that vonoprazan was potent for the management of ESD ulcers although lansoprazole was also sufficient and cost-effective.

### Terminology

Vonoprazan is a potent option for the management of ESD-induced ulcers.

### Peer-review

This article is relatively novel. There is no report on the drug used to treat the post-ESD ulcers. These results are thought to be very useful article from the terms of cost effective.

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