ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2023 June 16; 15(6): 420-490

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Endoscopy

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INDEXING/ABSTRACTING

The *WJGE* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 Journal Citation Indicator (JCI) for *WJGE* as 0.33.

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Production Editor: *Yi-Xuan Cai*; **Production Department Director:** *Xu Guo*; **Editorial Office Director:** *Jia-Ping Yan*.

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Anastasios Koulaouzidis, Bing Hu, Sang Chul Lee, Joo Young Cho

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5190/editorialboard.htm

PUBLICATION DATE
June 16, 2023

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

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https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
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ONLINE SUBMISSION
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World Journal of Gastrointestinal Endoscopy

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World J Gastrointest Endosc 2023 June 16; 15(6): 420-433

DOI: 10.4253/wjge.v15.i6.420

ISSN 1948-5190 (online)

EVIDENCE REVIEW

Applications of endoscopic vacuum therapy in the upper gastrointestinal tract

Konstantinos Kouladouros

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Sano W, Japan; Spadaccini M, Italy

Received: April 3, 2023
Peer-review started: April 3, 2023
First decision: May 12, 2023
Revised: May 15, 2023
Accepted: June 2, 2023
Article in press: June 2, 2023
Published online: June 16, 2023

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Abstract

Endoscopic vacuum therapy (EVT) is an increasingly popular treatment option for wall defects in the upper gastrointestinal tract. After its initial description for the treatment of anastomotic leaks after esophageal and gastric surgery, it was also implemented for a wide range of defects, including acute perforations, duodenal lesions, and postbariatric complications. Apart from the initially proposed hand-made sponge inserted using the "piggyback" technique, further devices were used, such as the commercially available EsoSponge and VAC-Stent as well as open-pore film drainage. The reported pressure settings and intervals between the subsequent endoscopic procedures vary greatly, but all available evidence highlights the efficacy of EVT, with high success rates and low morbidity and mortality, so that in many centers it is considered to be a first-line treatment, especially for anastomotic leaks.

Key Words: Negative pressure therapy; Vacuum therapy; Anastomotic leak; Perforation; Oesophagus; Stent

Core Tip: Endoscopic vacuum therapy (EVT) is a novel and effective endoscopic treatment option for anastomotic leaks and perforations in the upper gastrointestinal tract. Through the wide variety of available materials, EVT can be individually applied in almost every part of the oesophagus, the stomach and the duodenum with a clinical success rate of > 80% and low morbidity and mortality.

Citation: Kouladouros K. Applications of endoscopic vacuum therapy in the upper gastrointestinal tract. *World J Gastrointest Endosc* 2023; 15(6): 420-433
URL: https://www.wjgnet.com/1948-5190/full/v15/i6/420.htm
DOI: https://dx.doi.org/10.4253/wjge.v15.i6.420

INTRODUCTION

The endoscopic treatment of wall defects in the upper gastrointestinal tract, both postoperative and acute/iatrogenic, is a challenging task for the endoscopist and requires a deep understanding of the pathophysiologic mechanisms involved as well as a high degree of expertise. The surgical approach, involving the closure of the defect and external drainage of the infected cavity, is technically challenging and associated with high morbidity and mortality, especially in difficult anatomic areas such as the intrathoracic esophagus and the duodenum[1,2]. The necessity of minimally invasive alternatives was therefore evident very early and various endoscopic methods have been implemented throughout the years, including endoscopic lavage, transmural drainage, and defect closure with clips, suturing, and stents[3]. Endoscopic vacuum therapy (EVT) was recently added to the spectrum of minimally invasive therapeutic options and quickly gained popularity, especially in Europe, mainly because of its tailored approach and its very good outcomes in a wide range of situations[4].

In this narrative review, we discuss the indications, technical aspects, and outcomes of EVT based on the current literature.

BASIC PRINCIPLES AND ESTABLISHMENT OF EVT

Vacuum therapy was initially introduced by plastic surgeons as a treatment option for chronic, infected, and ischemic wounds[5]. Its basic principle is that negative pressure applied to a secondary healing wound through a sealed system of a sponge applied onto the wound, with an airtight film covering it and a suction pump connected to it by a tube, accelerates the healing process through multiple mechanisms including: (1) Increased blood flow; (2) Local modulation of cytokines and chemoreceptor-modulated cell signaling, leading to enhanced neoangiogenesis and increased formation of granulation tissue; (3) Removal of debris and microorganisms; (4) Reduction of interstitial edema; (5) Continuous drainage of wound secretions; and (6) Macrodeformation of the wound with approximation of its edges and reduction of its volume[4-7].

After its initial application, the system needs to be changed regularly until adequate healing of the wound is achieved. Vacuum therapy quickly became an established treatment option for external wounds and in 2003 the first attempt was made to implement its principles for the treatment of an anastomotic leak in the rectum, practically treating the infected mesorectal cavity behind the anastomotic dehiscence as a chronic wound[8]. For that purpose, the sponge was mounted to a drain tube and then endoscopically inserted through the defect and into the cavity. Upon application of a vacuum to the other end of the tube, the cavity collapsed around the sponge, thus sealing the system without the need for a covering film. After the first successful implementation of EVT in the rectum, it started becoming popular for the treatment of rectal anastomotic leaks, and in 2008 it was used for the first time for similar defects in the upper gastrointestinal tract[9,10]. Initially, the method was only used in German centers. After the encouraging results of the first case series were published in subsequent years, EVT started to gain popularity and the first international reports from the United States and Korea were published in 2016, thus paving the way for its worldwide acceptance as a viable treatment option for defects of the gastrointestinal tract[11-14].

The main advantages of this novel approach in comparison to the already existing endoscopic treatment options, such as clips and stents, are its ability to facilitate the secondary healing of the defect without forcing an adaptation of the rigid, inflamed, and fibrotic edges and the possibility not only to cover the defect but also to properly drain the cavity behind it without the need for further external drainage. Disadvantages include the necessity of multiple endoscopic procedures, patient discomfort due to the transnasal tube, and reduced or prohibited oral intake because of the occlusion of the gastrointestinal tract, especially in the case of intraluminally placed devices.

INDICATIONS

EVT can be applied for all wall defects in the upper gastrointestinal tract as long as the following two conditions are fulfilled: There is adequate blood perfusion around the defect to allow for the tissue to react to the negative pressure, and there is a closed compartment that can collapse around the negative pressure device[15]. Although the size of the defect and the cavity plays an important role in the

planning of the initial application and the duration of the therapy, large cavities and defects are not considered a contraindication. In one of the first published case series of Loske *et al*[11] in 2010 the size of the cavity was 3-40 mm, however recently published data have proven the feasibility of EVT in cavities > 7 cm and up to 15 cm, as long as they are closed and can collapse around the negative pressure device[11,16]. A large defect is associated with more intraprocedural difficulties and an increased number of procedures but also does not affect the outcomes of EVT[17].

Type of defect

The most common indications for EVT in the upper gastrointestinal tract are anastomotic leaks and acute perforations[18].

Anastomotic leaks after upper gastrointestinal tract surgery were the first indications for EVT described in the initial reports[9,10]. The incidence of anastomotic leaks after esophageal and gastric resections, typically presenting 7-10 d postoperatively, ranges between 5%-30% and is associated with increased morbidity and mortality rates of between 20%-50%[1,19,20]. In a Dutch cohort study including 1282 esophageal resections, an anastomotic leak was identified as the predominant specific complication associated with 30-d and 90-d mortality[21]. Surgical revision after esophagectomy has been associated with mortality of up to 64% and usually results in esophageal discontinuity[1,2]. Additionally, reversing esophageal discontinuity is not possible in 30% of the patients and even if it is attempted, it is associated with morbidity rates of up to 68%, long-term dysphagia in almost half of the patients, and sometimes the necessity of multiple surgical revisions[22-24]. Therefore, various conservative and minimally invasive regimes have been suggested, including thoracic drains and antibiotics, endoscopically placed transnasal drains, transmural drains (double-pigtail stents), defect adaptation with clips and suturing devices, and bridging of the leak with fully covered stents[25-29]. And yet, as Murphy pointed out in an editorial in 2010, the increasing number of treatment options for anastomotic dehiscence after esophagectomy reflects the difficulty in realizing a definitive therapy[3]. The introduction of EVT offered a powerful tool in the hands of the endoscopists, since it combines coverage of the defect and adequate drainage of the cavity behind the leak without the necessity of an additional, external drain and presented success rates of between 78%-100%[11,30-32]. Initially, EVT was used as a rescue therapy after failed surgical revision or stenting, but currently, it is being used as a first-line treatment for anastomotic leaks in many high-volume centers for upper gastrointestinal tract surgery[9,10,32]. Nevertheless, the endoscopist must bear in mind that although EVT can be applied for most anastomotic leaks, it is not suitable for very early leaks (within 4 d after surgery) with massive or complete anastomotic rupture and excessive tissue necrosis, and these patients should undergo surgical revision[30,32].

Acute perforations are nowadays usually iatrogenic and rarely spontaneous or traumatic. In contrast with anastomotic leaks, the edges of acute perforations are usually clean and lack inflammatory and fibrotic alterations, thus allowing for a better adaptation[33]. Additionally, no large cavity has been formed yet behind the defect. Therefore, closure of the perforation should be the primary therapeutic goal. Gomez-Esquivel suggested a therapeutic algorithm, according to which defects up to 2 cm should be primarily closed using though-the-scope clips. For defects between 2-3 cm over-the-scope-clips could be a better option and even larger defects should be covered by stents, as long as there is no cavity formed behind the defect. In the presence of a cavity, EVT should be considered the primary therapeutic option[34]. Early findings on the use of EVT for iatrogenic perforations and Boerhaave's syndrome also showed a very high success rate of up to 100% with a minimum duration of therapy, but they are mostly based on small case series since in most centers EVT is considered a second-line treatment for acute perforations and thus is not as commonly implemented[35-37].

Localisation

EVT has been reportedly used in all parts of the upper gastrointestinal tract and its feasibility and outcomes are primarily tied to technical aspects, including correct positioning of the device and the environment of the cavity.

The application of EVT for defects of the esophagus and intrathoracic anastomoses after esophageal surgery is the most commonly reported use[11,30]. The defects are usually easily reachable, and the associated cavities are restricted inside the mediastinum, thus facilitating the placement of the EVT device. Additionally, the high risk associated with esophageal emergency surgery and redo surgery further highlights the importance of EVT as a primary treatment in these cases[1]. Defects of the proximal esophagus have been described to be particularly difficult to treat, since negative pressure is more difficult to establish and maintain and the patient discomfort is maximized through the presence of a foreign body so close to the upper esophageal sphincter[4]. Nevertheless, several reports have demonstrated its feasibility, not only in the upper esophagus but also for pharyngeal defects after head and neck surgery[38,39].

Intraperitoneal gastric defects communicating with the abdominal cavity are typically not suitable for EVT and surgery should be preferred instead[4]. Additionally, intraluminal EVT is technically very difficult in the stomach, since its volume does not allow for the precise positioning of the EVT device in front of the defect and the complete collapse of the organ around it. Nevertheless, in the presence of a well-defined abscess cavity around an anastomotic leak or perforation it can be implemented, especially

for patients showing poor tissue healing or who are unsuitable for surgery[40,41].

A special subgroup of gastric defects is those occurring after bariatric surgery. Staple line leaks occur in 1%-2% of patients after sleeve gastrectomy and 2%-5% of patients after Roux-en-Y gastric bypass[42,43]. Especially in the case of sleeve gastrectomy, leaks mostly occur at the proximal end of the staple line and are caused when the intragastric pressure exceeds the staple line resistance, whereas true ischemic leaks are rare[44,45]. Such leaks are characterized by a late onset of mild symptoms with up to 50% being asymptomatic, probably because of the amount of visceral fat restricting the leak and preventing generalized peritonitis[46,47]. Revision surgery after the second postoperative day has been proven to have insufficient results, thus shifting the focus toward endoscopic treatment options[46]. Several small series have reported the feasibility of EVT in these cases since 2016 and a recent analysis of 31 patients as well as a meta-analysis of 5 studies with a total of 55 patients showed high success rates of between 87%-90%[46,48].

Duodenal defects are technically more challenging and make the material selection more important. The long distance of the defect from the teeth is the main restricting factor when using an overtube, whereas the passage of the pyloric sphincter and the poor maneuverability of the endoscope inside the duodenum makes the positioning of a sponge in the piggyback technique more difficult. The slenderer variation of the open-pore film drainage (OFD), further explained below, can be placed more easily and seems to be an adequate alternative[49,50]. If technically feasible, EVT has been reported to have equally high success rates for duodenal defects, including perforations after endoscopic resections or endoscopic retrograde cholangiopancreatography and leaks after suture of perforated ulcers and intraoperative injuries, partially due to the additional benefit of removing the gastric and duodenal secretions from the area of the defect, which could potentially inhibit the healing process[50-53].

The use of EVT for rare indications, such as esophagobronchial fistulas and pancreatic necrosis has also been reported, but the evidence available is still insufficient[54,55].

TECHNICAL ASPECTS

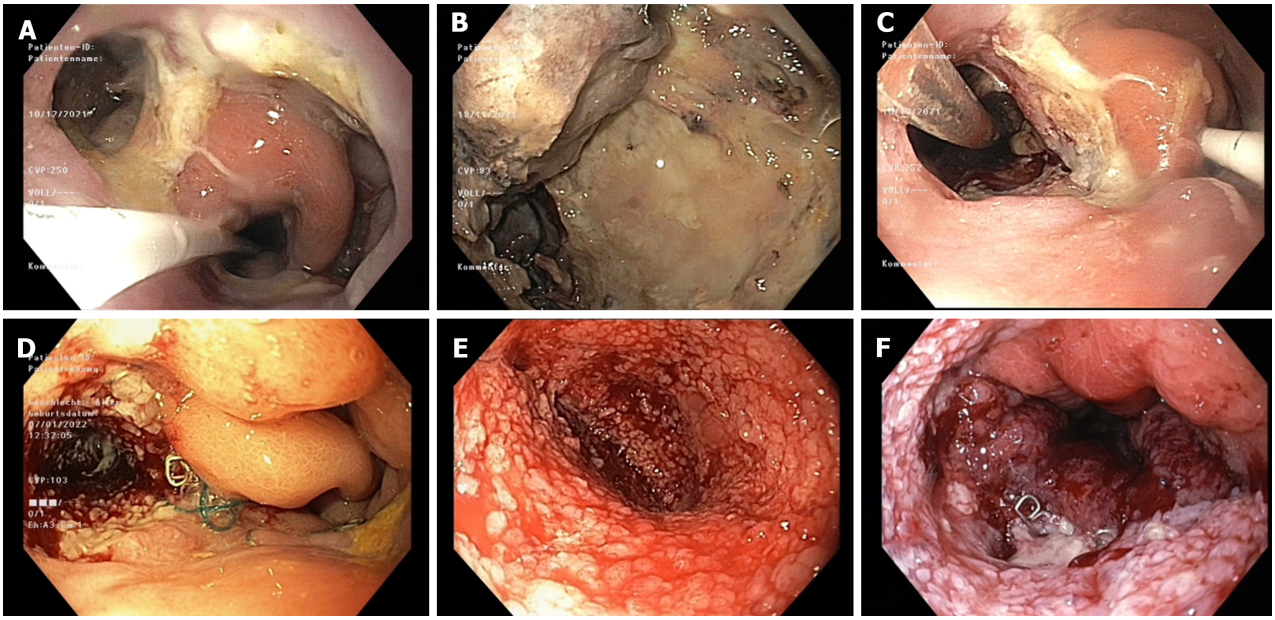
Preprocedural preparation

A combination of endoscopy and imaging techniques – most commonly computed tomography (CT) with oral contrast – is usually used to diagnose the defects and set the indication for EVT[4]. A careful endoscopic examination and documentation of the defect, the cavity behind it, and the blood perfusion around it are crucial for the planning of the initial procedure and the monitoring of the effects of EVT during the treatment[11]. CT scan provides additional information regarding the size and geometry of the cavity as well as its proximity to delicate anatomic structures, including the lung and large vessels.

Intracavitary or intraluminal?

The ideal placement of the EVT device has been thoroughly discussed in the literature. Traditional EVT consists of placing a sponge through the defect of the wall and inside the extraluminal cavity. The applied negative pressure causes the cavity to collapse, allows for sufficient drainage, and induces the formation of granular tissue on the walls of the cavity. During the subsequent EVT system changes the sponge is gradually retracted towards the lumen, thus leading to a downsizing of the cavity and finally to a closure of the defect (Figure 1). Alternatively, if the defect is too small, the EVT device can be placed intraluminally in front of it and the negative pressure is transferred to the cavity through the defect. Most experts suggest that, whenever technically possible, intracavitary EVT should be preferred, since it better reaches the entire cavity, thus enabling the healing from its most distal parts towards the lumen. At the same time, it prevents a superficial closure of the defect prior to the obliteration of the cavity with the formation of a closed, insufficiently drained space and ultimately an abscess[11,15,46,56-59]. Even in case of small wall defects, a prior balloon dilatation should be performed to enable the intracavitary placement of the EVT device, if a larger cavity is suspected[32]. A recent retrospective study with 119 patients also showed, that intraluminal placement of the EVT device is an independent risk factor for treatment failure, further supporting this strategy[60]. A further disadvantage of the intraluminal placement of the sponge is the complete occlusion of the lumen. As for the exact placement of the sponge inside the cavity, Loske *et al*[11] suggested that a small sponge at the entrance of the cavity is enough and can cause the entire cavity to collapse around it[11]. However, in this report, the maximum size of the cavities was 4 cm. In the case of larger cavities, this positioning could lead to a collapse of the proximal part of the cavity around the sponge with subsequent formation of granular tissue and gradual closure, thus separating the most distal parts and forming a second, insufficiently drained cavity. Therefore, we suggest the placement of a larger sponge up to the most distal part of the cavity during the initial procedure and a gradual withdrawal towards the lumen in the subsequent changes, in order to facilitate the gradual closure of the cavity from distal to proximal[16].

In case an intracavitary positioning is not possible and an intraluminal EVT has to be applied, a CT scan should be performed to exclude the presence of an insufficiently drained cavity, especially if the size of the defect does not allow for a thorough endoscopic exploration. A combination of both methods, simultaneously or in succession according to the changing geometry of the defect, is also possible.



DOI: 10.4253/wjge.v15.i6.420

Figure 1 Intracavitary endoscopic vacuum therapy for an anastomotic leak after Ivor-Lewis esophagectomy. A: 10 mm wide Anastomotic leak; B: 6 cm deep cavity with necrotic tissue, debris, and fibrin; C: Intracavitary positioning of an EsoSponge (a nasojejunal feeding tube is visible inside the lumen to the right); D: Downsizing of the defect after the first endoscopic vacuum therapy (EVT) session; E: Clean cavity with healthy granular tissue after the first EVT session; F: Healed anastomotic leak after 4 EVT sessions.

Materials

The basic EVT system consists of the actual EVT device, usually a sponge or a drain, that is placed in the area where the negative pressure should be applied, an external negative pressure source, which may be a drain suction bottle or a pump, and tubing that connects these two elements and transfers the negative pressure from the external source to the EVT device. Regarding the negative pressure source, drain suction bottles are cheap and widely available, but the suction force they apply is unreliable and more difficult to control. Electronic pumps offer better control of the applied negative pressure; however, it has to be pointed out that most of the commercially available pumps are designed for and dedicated to external vacuum therapy and small adaptations are usually necessary to make them compatible with EVT devices[4].

Regarding the EVT device, a large variety of alternatives has been suggested and the selection is usually based on the anatomic configuration of the defect, the availability of materials, and the experience of the endoscopist. In the initial description of endoscopic negative pressure therapy an individually prepared sponge was inserted using the "piggyback" technique[10]. According to this technique, a piece of polyurethane sponge designed for external negative pressure therapy is cut to the size of the cavity and attached around the perforated end of a surgical drain or a nasogastric tube (Figure 2). Macroporous, low-density sponges are preferred because of their greater debriding capacity and their stronger contraction under negative pressure, which leads to a more pronounced shrinkage of the cavity, although this structure allows for more tissue ingrowth thus making removal more difficult [4]. The distal end of the drain is shortened accordingly so that no perforations lie outside of the sponge. An endoscopic forceps is inserted into the instrument channel of the endoscope and the tip of the sponge or a loop attached to its distal end is grasped. The sponge is then inserted parallel to the endoscope and placed, with the use of the forceps, in its proper position. This method is cheap and versatile, allowing for the individual construction of the sponge according to the needs of every patient. However, the "piggyback" technique is technically demanding and the parallel insertion of the sponge and the endoscope restricts the field of view and might increase the risk of injury, especially in organs with a narrow lumen, like the esophagus. This method was predominantly used in earlier studies and is still being used in many centers with high success rates[32,57,58,60].

The EsoSponge System (B. Braun Medical Ltd, Sheffield, United Kingdom) became available in 2014 as a variation of the EndoSponge System designed for rectal EVT and is still the only commercially available EVT sponge. It consists of a 55 mm long, 15 mm wide macroporous sponge fixed at the end of a 100 cm drainage tube, an overtube, and a pusher (Figure 2). The endoscope is inserted into the overtube and then inserted through the defect into the cavity. The overtube is slid over the endoscope until its tip is inside the cavity and then the endoscope is removed, leaving the overtube in place. The sponge is inserted into the overtube and pushed through it with the help of the pusher. When the entire pusher is inside the overtube, the sponge has been completely released in front of the tip of the overtube and inside the cavity. In the case of intraluminal EVT the tip of the overtube is placed inside the lumen,

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Figure 2 Endoscopic vacuum therapy materials. A: The necessary materials for a handmade endoscopic vacuum therapy (EVT) sponge: Suture, scissors, needleholder, drain and polyurethane sponge; B: The components of the EsoSponge System: EVT sponge, pusher and overtube; C: A comparison of a handmade EVT sponge (left) and an EsoSponge (right).

directly proximal to the defect, and the sponge is released in the lumen, at the entrance of the cavity. The position of the sponge is controlled endoscopically and corrected if necessary. This procedure is standardized and technically easier to perform, while the overtube protects the esophageal wall from potential injuries and separates the gastrointestinal tract from the airway, thus reducing the risk of aspiration. The sponge can also be modified according to the geometry of each cavity and even extended with the attachment of additional pieces of sponge if necessary[16]. Large retrospective studies have shown high success rates with the use of the EsoSponge System, however, none compare it to the "piggyback" technique, so the final decision lies at the discretion of the endoscopist[11,30,52,61,62].

In 2015 Loske *et al*[49] described the OFD tool, an alternative EVT device consisting of a nasogastric tube with its distal, perforated end wrapped in a very thin, double-layered, open-pore drainage film (Figure 3). The drainage film is fixed around the tube with a suture, the tube is inserted through the nose like a normal nasogastric tube and the distal tip is positioned through the defect or in front of it with the use of an endoscopic forceps[49]. This device is much smaller than the sponges, can be easily placed through smaller defects or in difficult positions, like the duodenum, and can be left in place longer, since it is not as prone to tissue ingrowth as other devices. The first reports on OFD have shown encouraging results for various indications, including duodenal lesions and preemptive EVT after esophageal resection[63-65].

A further development was the introduction of the VAC-Stent (MICRO-TECH Europe GmbH, Düsseldorf, Germany), a fully covered, 70 mm long and 14 mm wide self-expanding metal stent (SEMS) with its central 50 mm part covered by a macroporous polyurethane sponge connected to a tube that can be connected to a negative pressure source (Figure 4). This product combines the advantages of intraluminal EVT with a lack of occlusion of the gastrointestinal lumen, thus allowing oral intake and reducing patient discomfort. Since it can only be placed intraluminally, it is suitable for defects without large associated cavities, although it can also be placed over an intracavitary sponge, combining both methods. The first published series showed a success rate of 80%, although a prominent selection bias of these studies has to be taken into consideration[66,67].

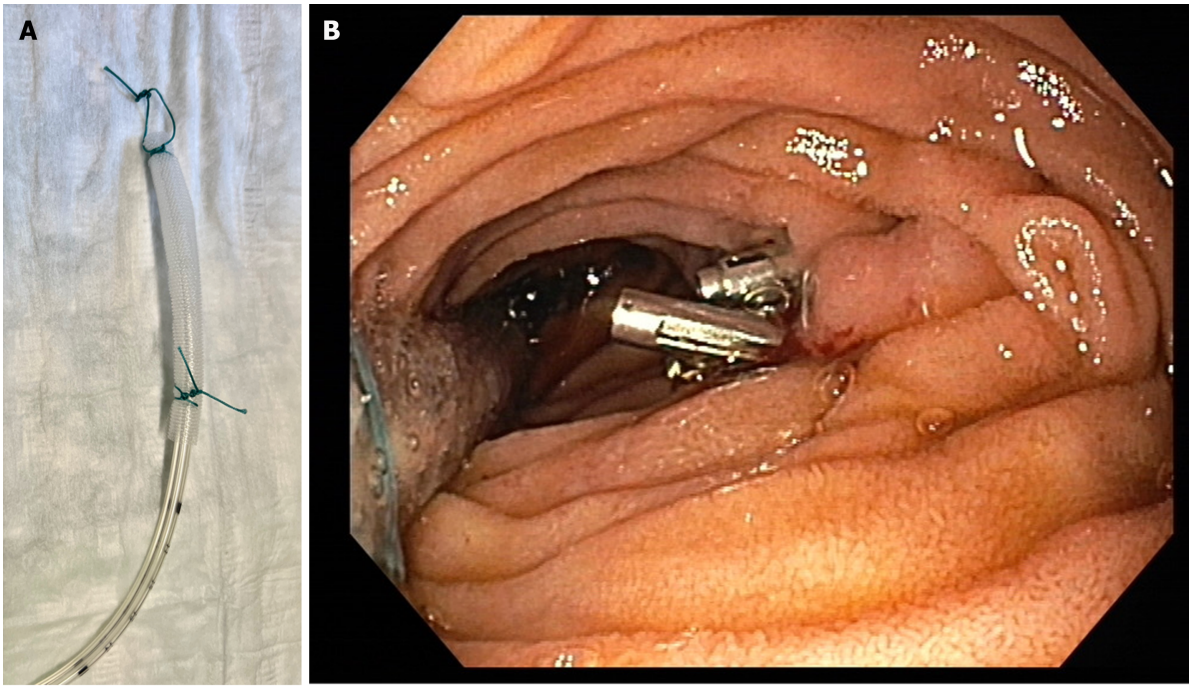

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Figure 3 Open-pore film drainage. A: The open-pore film drainage (OFD) system; B: Intraluminal application of OFD in the duodenum after a resection related perforation (clips are visible at the resection site).

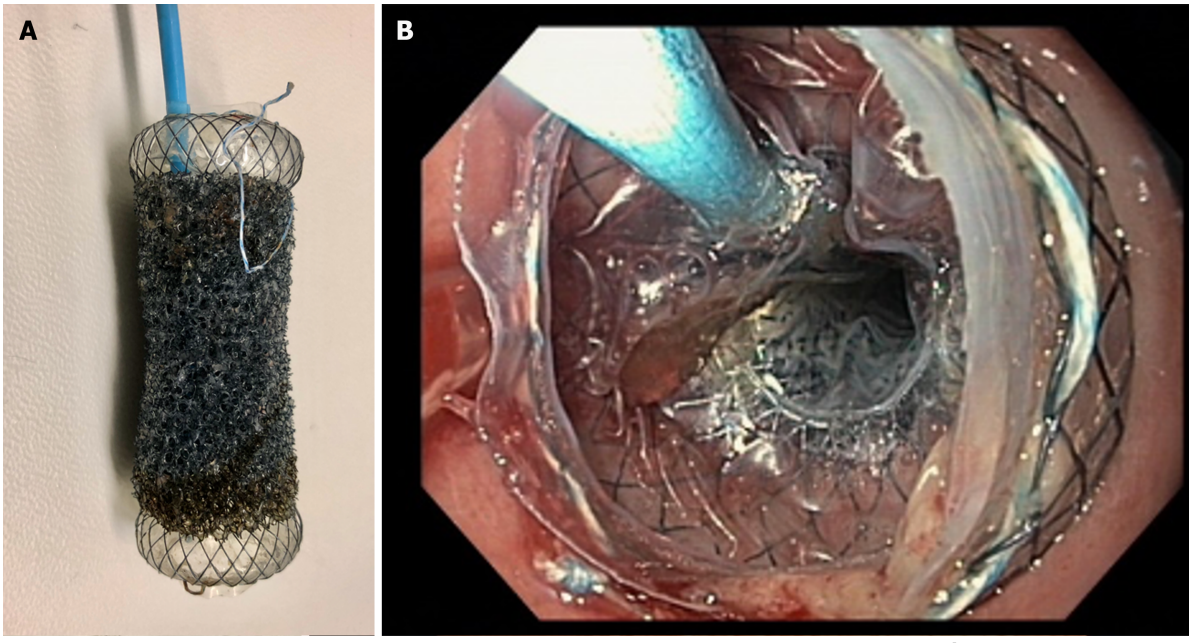

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Figure 4 VAC-Stent (MICRO-TECH Europe GmbH, Düsseldorf, Germany). A: The VAC-Stent system; B: The VAC-stent in place in the esophagus.

Postprocedural care, settings, and re-interventions

The initial placement of the EVT device and the subsequent procedures can be performed in the endoscopy suite under sedation, provided that the patient's condition supports that. The initial procedure takes usually slightly longer than the following ones and the average procedure time is between 30-60 min[68,69]. The partial or complete occlusion of the lumen is an important issue and the placement of a feeding tube distal to the EVT device is generally advised. Especially in the case of Ivor-Lewis esophagectomy with delayed gastric emptying the placement of a dual-lumen tube should be considered, with the longer feeding tube positioned postpyloric and the proximal gastric tube in the stomach to facilitate the evacuation of gastric secretions[30].

There is no consensus regarding the settings of the negative pressure, mainly because of the complete lack of evidence on this subject. Initially the pressure of -125 mmHg usually used in external negative pressure therapy was also used for EVT and pressure settings between -100 and -125 mmHg have been used in the largest published series to date[30,32,60]. Other authors suggest lower pressure settings of -20 to -50 mmHg in order to prevent bleeding, injuries, and formation of fistulas, especially when the EVT device lies in close proximity to delicate structures[70]. Still, the standard pressure settings vary greatly from center to center and this was also depicted in an international survey published in 2019[59].

A further issue subject to a lot of debate is the ideal interval between changes of the EVT system. It is known from external negative pressure therapy that the sponge becomes occluded by tissue ingrowth and wound secretions and has to be changed regularly. Most of the experts suggest an interval of 3-5 d [15,59,71]. However, the lack of further evidence has led to a wide spread of different strategies used in different centers and this is also depicted in the literature, with some authors supporting a shorter interval of 2-3 d so as to prevent excessive tissue ingrowth and others opting for an interval of 7 d, aiming to reduce the number of procedures needed[60,61,72,73]. Intervals over 7 d are generally discouraged, since the sponge might be embedded in the tissue thus making its removal difficult and increasing the risk of injuries, but apart from that the decision is usually made according to center standards and individual patient characteristics[7].

The negative pressure has to be relieved prior to any subsequent endoscopic procedure in order to facilitate the removal of the sponge. If the device is firmly attached to the tissue, it may be rinsed with water and then carefully dislodged from the surrounding tissue with the tip of the endoscope before being pulled back[58]. The defect and the cavity should be carefully reevaluated every time so that the therapy can be adapted accordingly. It has also been shown that the actual size of the defect or the cavity might not be evident during initial endoscopy, being masked behind debris or necrotic tissue, and only revealed in the subsequent procedures[16].

The main criterion for termination of EVT is the formation of a shallow cavity with a wide entrance and adequate drainage into the lumen, covered by healthy granular tissue[13,16]. The exact maximum cavity size required to end EVT varies between 0.5 and 3 cm from study to study, but geometry also plays an important role[74]. Additional treatment of residual defects and fistulas with the use of clips or fibrin glue has also been reported[32,75]. On the other hand, if no signs of tissue reaction and progress, both endoscopic and clinical, are evident after 3 wk of EVT, an alternative treatment should be considered[32].

OUTCOMES OF EVT

Published studies report success rates of EVT in the upper gastrointestinal tract ranging between 78%-100%, although most of them are retrospective and based on very heterogenous populations[30-32,46,62,76]. These findings have been verified in 3 meta-analyses with pooled success rates between 81%-87% [48,77,78]. When applied in the esophagus, clinical success seems to be higher for more distal defects and the results are better when applied as a first-line treatment in comparison to rescue treatment after failed stenting or surgical revision[62,77]. The type of defect does not seem to affect the success rate, although acute perforations tend to need fewer procedures and a shorter overall duration of treatment [30,35].

The experience of the endoscopist is crucial for the technical and clinical success of EVT. A recent study evaluated outcomes in one clinic over a period of 10 years and noticed an increase in success rates from 80% to 91%, while therapy duration and the need for additional treatments and redo surgery significantly decreased with accumulating experience[17]. Ward *et al*[69] argued that technical proficiency can be achieved after the first 10 procedures, but this is largely dependent on the severity of the case and the geometry and localization of the defect[69].

The duration of treatment and the number of necessary procedures vary greatly and depend on the type of defect, the size of the defect and the associated cavity, and the healing potential of the patient. Most studies report 3-6 subsequent endoscopic procedures in a period of 11-25 d, with a tendency towards a shorter duration of treatment in cases of acute perforations and defects in the duodenum[14,30,32,35,52,76].

The rate of immediate adverse events is generally low and reaches 10% for the entire course of treatment[77]. These mostly include dislocation of the EVT device, mild bleeding after removal, and aspiration pneumonia[60]. Some rare but potentially life-threatening complications have been reported when the sponge came into close proximity to large vessels and eroded them, leading to uncontrolled and sometimes fatal bleeding, but to our knowledge, only 5 such cases have been reported so far[32,61,73]. Nevertheless, the severity of these complications points out the importance of careful evaluation of the cavity and, when in doubt, of an additional CT scan to assess the relative position of the sponge to delicate structures[32]. Bronchoesophageal fistulas have also been rarely reported, although in these cases it is difficult to differentiate if they were caused by EVT or the initial leak itself[57,79]. On the other hand, the most common long-term complications are strictures in the area affected by the EVT. The stricture rate lies between 8%-20%, but almost all of them can be successfully treated by endoscopic dilatation[60,61,77].

EVT AND ALTERNATIVE METHODS

A wide range of alternative treatments have been described for the treatment of upper gastrointestinal defects. Clips and suturing methods show high success rates in cases of acute perforations with small defects and no associated cavity[33,80]. Transluminal drainage with the use of transnasal tubes or pigtails has also been reported, but the evidence is still low and this method is mostly used in selected patients[27,29,81]. Stents are the most common treatment alternative to EVT. Until the introduction of EVT stenting was the primary treatment option for large defects and especially anastomotic leaks in the upper gastrointestinal tract, with clinical success rates between 80%-90%[28,82-84]. SEMS were used in most of the published studies and complications include stent migration, strictures, and aortoesophageal fistulas with potentially fatal bleeding[83,85,86]. The main disadvantage of SEMS, though, is the lack of drainage of the cavity behind the defect. Several retrospective studies and two metanalyses have compared treatment outcomes between EVT and SEMS, generally showing higher success rates, reduced duration of therapy, and lower rates of adverse events for EVT[57,75,87-90]. Only one study found no difference between the two treatment options in any of the parameters mentioned above; the cross-over between the two groups was however significant and might have influenced the results[91]. The protocol of the ESOLEAK study, a phase 2 randomized trial comparing EVT and SEMS in the upper gastrointestinal tract, was published in 2021. The study is currently recruiting and to our knowledge, no results have been published so far[92].

PREEMPTIVE EVT

Based on the fact that EVT facilitates healing, several efforts have been made to implement it prophylactically on high-risk anastomoses in order to reduce the incidence of anastomotic leaks. The main principle of preemptive EVT is that it can treat small, undetectable defects of the anastomosis and prevent the contamination of the mediastinum, thus leading to their closure before they become clinically evident[93]. In 2017 Neumann *et al*[94] suggested a scheduled endoscopic control of the anastomosis several days after esophagectomy with the application of preemptive EVT if the tissue showed any signs of ischemia. In this first series of 8 patients, the anastomotic leak rate was still 25% and 3 patients developed strictures[94]. Four further studies evaluated the intraoperative placement of a sponge or an OFD intraluminally at the area of the anastomosis and reevaluated 3-6 d later. In the case of high-risk findings during control-endoscopy, including visible suture material, fibrin, and ischemia, EVT was prolonged, otherwise it was terminated. The reported anastomotic leak rates varied between 0%-7.5%, which is lower than usually reported, but the series was small and there was no control group to verify its positive effects[65,93,95,96]. Therefore, preemptive EVT still remains an attractive theory, but further data is required to prove its efficacy and determine the patient groups that could profit from it.

CONCLUSION

In summary, we can conclude that EVT is an adequate treatment option for wall defects in the upper gastrointestinal tract, with high success rates and low morbidity. The available evidence has proved its efficacy in different localizations and clinical settings for both acute perforations and anastomotic leaks and especially for the latter it is considered a first-line treatment in many centers. However, the data regarding the technical aspects, including choice of materials, pressure settings, and procedure interval, are scarce, and further randomized trials are necessary to clarify those points.

FOOTNOTES

Author contributions: Kouladouros K performed the literature research, wrote and revised the manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Li L
L-Editor: A
P-Editor: Cai YX

REFERENCES

1 **Lang H**, Piso P, Stukenborg C, Raab R, Jähne J. Management and results of proximal anastomotic leaks in a series of 1114 total gastrectomies for gastric carcinoma. *Eur J Surg Oncol* 2000; **26**: 168-171 [PMID: 10744938 DOI: 10.1053/ejso.1999.0764]
2 **Orringer MB**. Reversing esophageal discontinuity. *Semin Thorac Cardiovasc Surg* 2007; **19**: 47-55 [PMID: 17403458 DOI: 10.1053/j.semtcvs.2006.11.004]
3 **Murphy T**, Jobe BA. Endoluminal management of anastomotic dehiscence after esophagectomy: an increasing quiver of options reflects the difficulty in realizing a definitive therapy. *Gastrointest Endosc* 2010; **71**: 387-389 [PMID: 20152315 DOI: 10.1016/j.gie.2009.09.033]
4 **Gutschow CA**, Schlag C, Vetter D. Endoscopic vacuum therapy in the upper gastrointestinal tract: when and how to use it. *Langenbecks Arch Surg* 2022; **407**: 957-964 [PMID: 35041047 DOI: 10.1007/s00423-022-02436-5]
5 **Argenta LC**, Morykwas MJ. Vacuum-assisted closure: a new method for wound control and treatment: clinical experience. *Ann Plast Surg* 1997; **38**: 563-76; discussion 577 [PMID: 9188971 DOI: 10.1097/00000637-199706000-00002]
6 **Glass GE**, Murphy GF, Esmaeili A, Lai LM, Nanchahal J. Systematic review of molecular mechanism of action of negative-pressure wound therapy. *Br J Surg* 2014; **101**: 1627-1636 [PMID: 25294112 DOI: 10.1002/bjs.9636]
7 **de Moura DTH**, de Moura BFBH, Manfredi MA, Hathorn KE, Bazarbashi AN, Ribeiro IB, de Moura EGH, Thompson CC. Role of endoscopic vacuum therapy in the management of gastrointestinal transmural defects. *World J Gastrointest Endosc* 2019; **11**: 329-344 [PMID: 31205594 DOI: 10.4253/wjge.v11.i5.329]
8 **Weidenhagen R**, Spelsberg F, Lang RA, Jauch KW, Gruetzner KU. A New Method for Sepsis Control Caused by Anastomotic Leakage in Rectal Surgery - the Endo-VAC. *Colorectal Disease* 2003; **5**: 1-4 [DOI: 10.1097/00024382-200403001-00608]
9 **Wedemeyer J**, Schneider A, Manns MP, Jackobs S. Endoscopic vacuum-assisted closure of upper intestinal anastomotic leaks. *Gastrointest Endosc* 2008; **67**: 708-711 [PMID: 18374029 DOI: 10.1016/j.gie.2007.10.064]
10 **Loske G**, Müller C. Endoscopic vacuum-assisted closure of upper intestinal anastomotic leaks. *Gastrointest Endosc* 2009; **69**: 601-2; author reply 602 [PMID: 19231507 DOI: 10.1016/j.gie.2008.06.058]
11 **Loske G**, Schorsch T, Müller C. Endoscopic vacuum sponge therapy for esophageal defects. *Surg Endosc* 2010; **24**: 2531-2535 [PMID: 20333402 DOI: 10.1007/s00464-010-0998-x]
12 **Leeds SG**, Burdick JS. Management of gastric leaks after sleeve gastrectomy with endoluminal vacuum (E-Vac) therapy. *Surg Obes Relat Dis* 2016; **12**: 1278-1285 [PMID: 27178614 DOI: 10.1016/j.soard.2016.01.017]
13 **Smallwood NR**, Fleshman JW, Leeds SG, Burdick JS. The use of endoluminal vacuum (E-Vac) therapy in the management of upper gastrointestinal leaks and perforations. *Surg Endosc* 2016; **30**: 2473-2480 [PMID: 26423414 DOI: 10.1007/s00464-015-4501-6]
14 **Hwang JJ**, Jeong YS, Park YS, Yoon H, Shin CM, Kim N, Lee DH. Comparison of Endoscopic Vacuum Therapy and Endoscopic Stent Implantation With Self-Expandable Metal Stent in Treating Postsurgical Gastroesophageal Leakage. *Medicine (Baltimore)* 2016; **95**: e3416 [PMID: 27100431 DOI: 10.1097/MD.0000000000003416]
15 **Loske G**, Müller CT. Tips and tricks for endoscopic negative pressure therapy. *Chirurg* 2019; **90**: 7-14 [PMID: 30280205 DOI: 10.1007/s00104-018-0725-z]
16 **Kouladouros K**, Belle S, Reissfelder C, Kähler G. Endoscopic negative pressure therapy for leaks with large cavities in the upper gastrointestinal tract: is it a feasible therapeutic option? *Scand J Gastroenterol* 2021; **56**: 193-198 [PMID: 33332197 DOI: 10.1080/00365521.2020.1861645]
17 **Reimer S**, Lock JF, Flemming S, Weich A, Widder A, Plaßmeier L, Döring A, Hering I, Hankir MK, Meining A, Germer CT, Groneberg K, Seyfried F. Endoscopic Management of Large Leakages After Upper Gastrointestinal Surgery. *Front Surg* 2022; **9**: 885244 [PMID: 35615653 DOI: 10.3389/fsurg.2022.885244]
18 **Schorsch T**, Müller C, Loske G. Endoscopic vacuum therapy of anastomotic leakage and iatrogenic perforation in the esophagus. *Surg Endosc* 2013; **27**: 2040-2045 [PMID: 23247743 DOI: 10.1007/s00464-012-2707-4]
19 **Alanezi K**, Urschel JD. Mortality secondary to esophageal anastomotic leak. *Ann Thorac Cardiovasc Surg* 2004; **10**: 71-75 [PMID: 15209546]
20 **Ikeguchi M**, Oka S, Gomyo Y, Tsujitani S, Maeta M, Kaibara N. Postoperative morbidity and mortality after gastrectomy for gastric carcinoma. *Hepatogastroenterology* 2001; **48**: 1517-1520 [PMID: 11677999]
21 **Talsma AK**, Lingsma HF, Steyerberg EW, Wijnhoven BP, Van Lanschot JJ. The 30-day versus in-hospital and 90-day mortality after esophagectomy as indicators for quality of care. *Ann Surg* 2014; **260**: 267-273 [PMID: 25350650 DOI: 10.1097/SLA.0000000000000482]
22 **Barkley C**, Orringer MB, Iannettoni MD, Yee J. Challenges in reversing esophageal discontinuity operations. *Ann Thorac Surg* 2003; **76**: 989-94; discussion 995 [PMID: 14529973 DOI: 10.1016/S0003-4975(03)00825-7]
23 **Braghetto I**, Cardemil G, Csendes A, Venturelli A, Herrera M, Korn O, Sepúlveda S, Rojas J. Digestive tract reconstitution after failed esophago-gastro or esophago-coloanastomosis. *Arq Bras Cir Dig* 2013; **26**: 7-12 [PMID: 23702863 DOI: 10.1590/S0102-67202013000100003]
24 **Parekh K**, Iannettoni MD. Complications of esophageal resection and reconstruction. *Semin Thorac Cardiovasc Surg*

2007; **19**: 79-88 [PMID: 17403462 DOI: 10.1053/j.semtcvs.2006.11.002]

25 **Matory YL**, Burt M. Esophagogastrectomy: reoperation for complications. *J Surg Oncol* 1993; **54**: 29-33 [PMID: 8377501 DOI: 10.1002/jso.2930540109]

26 **Nguyen NT**, Hinojosa MW, Fayad C, Wilson SE. Minimally invasive management of intrathoracic leaks after esophagogastrectomy. *Surg Innov* 2007; **14**: 96-101 [PMID: 17558014 DOI: 10.1177/1553350607303210]

27 **Hu Z**, Yin R, Fan X, Zhang Q, Feng C, Yuan F, Chen J, Jiang F, Li N, Xu L. Treatment of intrathoracic anastomotic leak by nose fistula tube drainage after esophagectomy for cancer. *Dis Esophagus* 2011; **24**: 100-107 [PMID: 20819102 DOI: 10.1111/j.1442-2050.2010.01102.x]

28 **Amrani L**, Ménard C, Berdah S, Emungania O, Soune PA, Subtil C, Brunet C, Grimaud JC, Barthet M. From iatrogenic digestive perforation to complete anastomotic disunion: endoscopic stenting as a new concept of "stent-guided regeneration and re-epithelialization". *Gastrointest Endosc* 2009; **69**: 1282-1287 [PMID: 19286179 DOI: 10.1016/j.gie.2008.09.043]

29 **Jung CFM**, Hallit R, Müller-Dornieden A, Calmels M, Goere D, Chaput U, Camus M, Gonzalez JM, Barthet M, Jacques J, Legros R, Barrioz T, Kück F, Seif Amir Hosseini A, Ghadimi M, Kunsch S, Ellenrieder V, Wedi E, Barret M. Endoscopic internal drainage and low negative-pressure endoscopic vacuum therapy for anastomotic leaks after oncologic upper gastrointestinal surgery. *Endoscopy* 2022; **54**: 71-74 [PMID: 33506454 DOI: 10.1055/a-1375-8151]

30 **Bludau M**, Fuchs HF, Herbold T, Maus MKH, Alakus H, Popp F, Leers JM, Bruns CJ, Hölscher AH, Schröder W, Chon SH. Results of endoscopic vacuum-assisted closure device for treatment of upper GI leaks. *Surg Endosc* 2018; **32**: 1906-1914 [PMID: 29218673 DOI: 10.1007/s00464-017-5883-4]

31 **Kuehn F**, Loske G, Schiffmann L, Gock M, Klar E. Endoscopic vacuum therapy for various defects of the upper gastrointestinal tract. *Surg Endosc* 2017; **31**: 3449-3458 [PMID: 28078463 DOI: 10.1007/s00464-016-5404-x]

32 **Laukoetter MG**, Mennigen R, Neumann PA, Dhayat S, Horst G, Palmes D, Senninger N, Vowinkel T. Successful closure of defects in the upper gastrointestinal tract by endoscopic vacuum therapy (EVT): a prospective cohort study. *Surg Endosc* 2017; **31**: 2687-2696 [PMID: 27709328 DOI: 10.1007/s00464-016-5265-3]

33 **Mennigen R**, Senninger N, Laukoetter MG. Novel treatment options for perforations of the upper gastrointestinal tract: endoscopic vacuum therapy and over-the-scope clips. *World J Gastroenterol* 2014; **20**: 7767-7776 [PMID: 24976714 DOI: 10.3748/wjg.v20.i24.7767]

34 **Gomez-Esquivel R**, Raju GS. Endoscopic closure of acute esophageal perforations. *Curr Gastroenterol Rep* 2013; **15**: 321 [PMID: 23558969 DOI: 10.1007/s11894-013-0321-9]

35 **Loske G**, Schorsch T, Dahm C, Martens E, Müller C. Iatrogenic perforation of esophagus successfully treated with Endoscopic Vacuum Therapy (EVT). *Endosc Int Open* 2015; **3**: E547-E551 [PMID: 26716109 DOI: 10.1055/s-0034-1392566]

36 **Loske G**, Schorsch T, van Ackeren V, Schulze W, Müller CT. Endoscopic vacuum therapy in Boerhaave's syndrome with open-pore polyurethane foam and a new open-pore film drainage. *Endoscopy* 2015; **47** Suppl 1 UCTN: E410-E411 [PMID: 26273785 DOI: 10.1055/s-0034-1392597]

37 **Loske G**, Schorsch T. [Endoscopic vacuum therapy for Boerhaave's syndrome]. *Chirurg* 2016; **87**: 676-682 [PMID: 27259548 DOI: 10.1007/s00104-016-0185-2]

38 **Lenzen H**, Negm AA, Erichsen TJ, Manns MP, Wedemeyer J, Lankisch TO. Successful treatment of cervical esophageal leakage by endoscopic-vacuum assisted closure therapy. *World J Gastrointest Endosc* 2013; **5**: 340-345 [PMID: 23858378 DOI: 10.4253/wjge.v5.i7.340]

39 **Loeck J**, von Lücken HJ, Münscher A, Müller CT, Loske G. Endoscopic negative pressure therapy (ENPT) in head and neck surgery: first experiences in treatment of postoperative salivary fistulas and cervical esophageal perforations. *Eur Arch Otorhinolaryngol* 2021; **278**: 4525-4534 [PMID: 33715018 DOI: 10.1007/s00405-021-06709-5]

40 **Loske G**, Lang U, Schorsch T, Müller CT. [Complex vacuum therapy of an abdominal abscess from gastric perforation : case report of innovative operative endoscopic management]. *Chirurg* 2015; **86**: 486-490 [PMID: 25995089 DOI: 10.1007/s00104-015-2993-1]

41 **Senne M**, Werner CR, Schempf U, Thiel K, Königsrainer A, Wichmann D. Comparison of Two Endoscopic Therapeutic Interventions as Primary Treatment for Anastomotic Leakages after Total Gastrectomy. *Cancers (Basel)* 2022; **14** [PMID: 35740645 DOI: 10.3390/cancers14122982]

42 **Noel P**, Nedelcu M, Gagner M. Impact of the Surgical Experience on Leak Rate After Laparoscopic Sleeve Gastrectomy. *Obes Surg* 2016; **26**: 1782-1787 [PMID: 26712495 DOI: 10.1007/s11695-015-2003-1]

43 **ASMBS Clinical Issues Committee**. ASMBS guideline on the prevention and detection of gastrointestinal leak after gastric bypass including the role of imaging and surgical exploration. *Surg Obes Relat Dis* 2009; **5**: 293-296 [PMID: 19356997 DOI: 10.1016/j.soard.2009.02.002]

44 **Baker RS**, Foote J, Kemmeter P, Brady R, Vroegop T, Serveld M. The science of stapling and leaks. *Obes Surg* 2004; **14**: 1290-1298 [PMID: 15603641 DOI: 10.1381/0960892042583888]

45 **Gagner M**, Buchwald JN. Comparison of laparoscopic sleeve gastrectomy leak rates in four staple-line reinforcement options: a systematic review. *Surg Obes Relat Dis* 2014; **10**: 713-723 [PMID: 24745978 DOI: 10.1016/j.soard.2014.01.016]

46 **Markus A**, Henrik BJ, Benedikt R, Alexander H, Thomas B, Clemens S, Jan-Hendrik E. Endoscopic vacuum therapy in salvage and standalone treatment of gastric leaks after bariatric surgery. *Langenbecks Arch Surg* 2022; **407**: 1039-1046 [PMID: 34787705 DOI: 10.1007/s00423-021-02365-9]

47 **Bhayani NH**, Swanström LL. Endoscopic therapies for leaks and fistulas after bariatric surgery. *Surg Innov* 2014; **21**: 90-97 [PMID: 23980200 DOI: 10.1177/1553350613497270]

48 **Intriago JMV**, de Moura DTH, do Monte Junior ES, Proença IM, Ribeiro IB, Sánchez-Luna SA, Bernardo WM, de Moura EGH. Endoscopic Vacuum Therapy (EVT) for the Treatment of Post-Bariatric Surgery Leaks and Fistulas: a Systematic Review and Meta-analysis. *Obes Surg* 2022; **32**: 3435-3451 [PMID: 35918596 DOI: 10.1007/s11695-022-06228-0]

49 **Loske G**, Rucktäschel F, Schorsch T, van Ackeren V, Stark B, Müller CT. Successful endoscopic vacuum therapy with

new open-pore film drainage in a case of iatrogenic duodenal perforation during ERCP. *Endoscopy* 2015; **47**: E577-E578 [PMID: 26649468 DOI: 10.1055/s-0034-1393388]

50 **Loske G**, Rucktaeschel F, Schorsch T, Moenkemueller K, Mueller CT. Endoscopic negative pressure therapy (ENPT) for duodenal leakage - novel repair technique using open-pore film (OFD) and polyurethane-foam drainages (OPD). *Endosc Int Open* 2019; **7**: E1424-E1431 [PMID: 31673614 DOI: 10.1055/a-0972-9660]

51 **Abbitt D**, Barnes AL, Hammad HT, Reveille RM, Jones EL. Endoluminal vacuum closure of a duodenal perforation. *J Surg Case Rep* 2021; **2021**: rjab479 [PMID: 34754414 DOI: 10.1093/jscr/rjab479]

52 **Chevallay M**, Lorenz F, Bichard P, Frossard JL, Schmidt T, Goeser T, Bruns CJ, Mönig SP, Chon SH. Outcome of endoscopic vacuum therapy for duodenal perforation. *Surg Endosc* 2023; **37**: 1846-1853 [PMID: 36241747 DOI: 10.1007/s00464-022-09686-w]

53 **Wichmann D**, Jansen KT, Onken F, Stüker D, Zerabruck E, Werner CR, Yurttas C, Thiel K, Königsrainer A, Quante M. Endoscopic negative pressure therapy as stand-alone treatment for perforated duodenal diverticulum: presentation of two cases. *BMC Gastroenterol* 2021; **21**: 436 [PMID: 34802417 DOI: 10.1186/s12876-021-02018-7]

54 **Loske G**, Schorsch T, Gobrecht O, Martens E, Rucktäschel F. Transgastric endoscopic vacuum therapy with a new open-pore film drainage device in a case of infective pancreatic necrosis. *Endoscopy* 2016; **48** Suppl 1: E148-E149 [PMID: 27116092 DOI: 10.1055/s-0042-106576]

55 **Kuckelman J**, Bryan D, Wiener D. Endoluminal Vacuum Therapy for Definitive Management of an Esophagobronchial Fistula. *Ann Thorac Surg* 2022; **113**: 669-673 [PMID: 34391698 DOI: 10.1016/j.athoracsur.2021.07.032]

56 **Loske G**, Schorsch T, Müller C. Intraluminal and intracavitary vacuum therapy for esophageal leakage: a new endoscopic minimally invasive approach. *Endoscopy* 2011; **43**: 540-544 [PMID: 21448855 DOI: 10.1055/s-0030-1256345]

57 **Brangewitz M**, Voigtländer T, Helfritz FA, Lankisch TO, Winkler M, Klempnauer J, Manns MP, Schneider AS, Wedemeyer J. Endoscopic closure of esophageal intrathoracic leaks: stent versus endoscopic vacuum-assisted closure, a retrospective analysis. *Endoscopy* 2013; **45**: 433-438 [PMID: 23733727 DOI: 10.1055/s-0032-1326435]

58 **Leeds SG**, Mencio M, Ontiveros E, Ward MA. Endoluminal Vacuum Therapy: How I Do It. *J Gastrointest Surg* 2019; **23**: 1037-1043 [PMID: 30671790 DOI: 10.1007/s11605-018-04082-z]

59 **Rodrigues-Pinto E**, Repici A, Donatelli G, Macedo G, Devière J, van Hooft JE, Campos JM, Galvao Neto M, Silva M, Eisendrath P, Kumbhari V, Khashab MA. International multicenter expert survey on endoscopic treatment of upper gastrointestinal anastomotic leaks. *Endosc Int Open* 2019; **7**: E1671-E1682 [PMID: 31788551 DOI: 10.1055/a-1005-6632]

60 **Jung DH**, Huh CW, Min YW, Park JC. Endoscopic vacuum therapy for the management of upper GI leaks and perforations: a multicenter retrospective study of factors associated with treatment failure (with video). *Gastrointest Endosc* 2022; **95**: 281-290 [PMID: 34555386 DOI: 10.1016/j.gie.2021.09.018]

61 **Ahrens M**, Schulte T, Egberts J, Schafmayer C, Hampe J, Fritscher-Ravens A, Broering DC, Schniewind B. Drainage of esophageal leakage using endoscopic vacuum therapy: a prospective pilot study. *Endoscopy* 2010; **42**: 693-698 [PMID: 20806153 DOI: 10.1055/s-0030-1255688]

62 **Richter F**, Hendricks A, Schniewind B, Hampe J, Heits N, von Schönfels W, Reichert B, Eberle K, Ellrichmann M, Baumann P, Egberts JH, Becker T, Schafmayer C. Eso-Sponge® for anastomotic leakage after oesophageal resection or perforation: outcomes from a national, prospective multicentre registry. *BJS Open* 2022; **6** [PMID: 35451010 DOI: 10.1093/bjsopen/zrac030]

63 **Loske G**, Schorsch T, Rucktaeschel F, Schulze W, Riefel B, van Ackeren V, Mueller CT. Open-pore film drainage (OFD): a new multipurpose tool for endoscopic negative pressure therapy (ENPT). *Endosc Int Open* 2018; **6**: E865-E871 [PMID: 29978007 DOI: 10.1055/a-0599-5886]

64 **Wichmann D**, Stüker D, Schempf U, Werner CR, Steger V, Königsrainer A, Schweizer U, Archid R. Endoscopic negative pressure therapy with open-pore film drainage and open-pore polyurethane sponge drainage for iatrogenic perforation of the esophagus. *Endoscopy* 2020; **52**: 377-382 [PMID: 32252093 DOI: 10.1055/a-1139-0772]

65 **Loske G**, Müller J, Schulze W, Riefel B, Müller CT. Pre-emptive active drainage of reflux (PARD) in Ivor-Lewis oesophagectomy with negative pressure and simultaneous enteral nutrition using a double-lumen open-pore film drain (dOFD). *Surg Endosc* 2022; **36**: 2208-2216 [PMID: 34973079 DOI: 10.1007/s00464-021-08933-w]

66 **Lange J**, Kähler G, Bernhardt J, Knievel J, Dormann A, Hügle U, Eisenberger CF, Heiss MM. The VACStent trial: combined treatment of esophageal leaks by covered stent and endoscopic vacuum therapy. *Surg Endosc* 2023; **37**: 3657-3668 [PMID: 36639580 DOI: 10.1007/s00464-023-09861-7]

67 **Chon SH**, Töx U, Lorenz F, Rieck I, Wagner BJ, Kleinert R, Fuchs HF, Goeser T, Quaas A, Bruns CJ. A Novel Hybrid Stent with Endoscopic Vacuum Therapy for Treating Leaks of the Upper Gastrointestinal Tract. *Visc Med* 2021; **37**: 403-409 [PMID: 34722723 DOI: 10.1159/000512320]

68 **Ooi G**, Burton P, Packiyanathan A, Loh D, Chen R, Shaw K, Brown W, Nottle P. Indications and efficacy of endoscopic vacuum-assisted closure therapy for upper gastrointestinal perforations. *ANZ J Surg* 2018; **88**: E257-E263 [PMID: 27860126 DOI: 10.1111/ans.13837]

69 **Ward MA**, Hassan T, Burdick JS, Leeds SG. Endoscopic vacuum assisted wound closure (EVAC) device to treat esophageal and gastric leaks: assessing time to proficiency and cost. *Surg Endosc* 2019; **33**: 3970-3975 [PMID: 30747284 DOI: 10.1007/s00464-019-06685-2]

70 **Jung CFM**, Müller-Dornieden A, Gaedcke J, Kunsch S, Gromski MA, Biggemann L, Seif Amir Hosseini A, Ghadimi M, Ellenrieder V, Wedi E. Impact of Endoscopic Vacuum Therapy with Low Negative Pressure for Esophageal Perforations and Postoperative Anastomotic Esophageal Leaks. *Digestion* 2021; **102**: 469-479 [PMID: 32045916 DOI: 10.1159/000506101]

71 **Loske G**. Endoscopic negative pressure therapy of the upper gastrointestinal tract. *Chirurg* 2019; **90**: 1-6 [PMID: 30456644 DOI: 10.1007/s00104-018-0727-x]

72 **Bludau M**, Hölscher AH, Herbold T, Leers JM, Gutschow C, Fuchs H, Schröder W. Management of upper intestinal leaks using an endoscopic vacuum-assisted closure system (E-VAC). *Surg Endosc* 2014; **28**: 896-901 [PMID: 24149851 DOI: 10.1007/s00464-013-3244-5]

73 **Pournaras DJ**, Hardwick RH, Safranek PM, Sujendran V, Bennett J, Macaulay GD, Hindmarsh A. Endoluminal Vacuum

Therapy (E-Vac): A Treatment Option in Oesophagogastric Surgery. *World J Surg* 2018; **42**: 2507-2511 [PMID: 29372375 DOI: 10.1007/s00268-018-4463-7]

74 **Sharp G**, Steffens D, Koh CE. Evidence of negative pressure therapy for anastomotic leak: a systematic review. *ANZ J Surg* 2021; **91**: 537-545 [PMID: 33480168 DOI: 10.1111/ans.16581]

75 **Mennigen R**, Harting C, Lindner K, Vowinkel T, Rijcken E, Palmes D, Senninger N, Laukoetter MG. Comparison of Endoscopic Vacuum Therapy Versus Stent for Anastomotic Leak After Esophagectomy. *J Gastrointest Surg* 2015; **19**: 1229-1235 [PMID: 25967140 DOI: 10.1007/s11605-015-2847-7]

76 **Zhang CC**, Liesenfeld L, Klotz R, Koschny R, Rupp C, Schmidt T, Diener MK, Müller-Stich BP, Hackert T, Sauer P, Büchler MW, Schaible A. Feasibility, effectiveness, and safety of endoscopic vacuum therapy for intrathoracic anastomotic leakage following transthoracic esophageal resection. *BMC Gastroenterol* 2021; **21**: 72 [PMID: 33593301 DOI: 10.1186/s12876-021-01651-6]

77 **Jung DH**, Yun HR, Lee SJ, Kim NW, Huh CW. Endoscopic Vacuum Therapy in Patients with Transmural Defects of the Upper Gastrointestinal Tract: A Systematic Review with Meta-Analysis. *J Clin Med* 2021; **10** [PMID: 34071877 DOI: 10.3390/jcm10112346]

78 **Tavares G**, Tustumi F, Tristão LS, Bernardo WM. Endoscopic vacuum therapy for anastomotic leak in esophagectomy and total gastrectomy: a systematic review and meta-analysis. *Dis Esophagus* 2021; **34** [PMID: 33479749 DOI: 10.1093/dote/doaa132]

79 **Hayami M**, Klevebro F, Tsekrekos A, Samola Winnberg J, Kamiya S, Rouvelas I, Nilsson M, Lindblad M. Endoscopic vacuum therapy for anastomotic leak after esophagectomy: a single-center's early experience. *Dis Esophagus* 2021; **34** [PMID: 33367786 DOI: 10.1093/dote/doaa122]

80 **Voermans RP**, Le Moine O, von Renteln D, Ponchon T, Giovannini M, Bruno M, Weusten B, Seewald S, Costamagna G, Deprez P, Fockens P; CLIPPER Study Group. Efficacy of endoscopic closure of acute perforations of the gastrointestinal tract. *Clin Gastroenterol Hepatol* 2012; **10**: 603-608 [PMID: 22361277 DOI: 10.1016/j.cgh.2012.02.005]

81 **Infante M**, Valente M, Andreani S, Catanese C, Dal Fante M, Pizzetti P, Giudice G, Basilico M, Spinelli P, Ravasi G. Conservative management of esophageal leaks by transluminal endoscopic drainage of the mediastinum or pleural space. *Surgery* 1996; **119**: 46-50 [PMID: 8560385 DOI: 10.1016/S0039-6060(96)80212-1]

82 **Evrard S**, Le Moine O, Lazaraki G, Dormann A, El Nakadi I, Devière J. Self-expanding plastic stents for benign esophageal lesions. *Gastrointest Endosc* 2004; **60**: 894-900 [PMID: 15605003 DOI: 10.1016/S0016-5107(04)02278-3]

83 **Dasari BV**, Neely D, Kennedy A, Spence G, Rice P, Mackle E, Epanomeritakis E. The role of esophageal stents in the management of esophageal anastomotic leaks and benign esophageal perforations. *Ann Surg* 2014; **259**: 852-860 [PMID: 24509201 DOI: 10.1097/SLA.0000000000000564]

84 **Kamarajah SK**, Bundred J, Spence G, Kennedy A, Dasari BVM, Griffiths EA. Critical Appraisal of the Impact of Oesophageal Stents in the Management of Oesophageal Anastomotic Leaks and Benign Oesophageal Perforations: An Updated Systematic Review. *World J Surg* 2020; **44**: 1173-1189 [PMID: 31686158 DOI: 10.1007/s00268-019-05259-6]

85 **Schweigert M**, Dubecz A, Stadlhuber RJ, Muschweck H, Stein HJ. Risk of stent-related aortic erosion after endoscopic stent insertion for intrathoracic anastomotic leaks after esophagectomy. *Ann Thorac Surg* 2011; **92**: 513-518 [PMID: 21592460 DOI: 10.1016/j.athoracsur.2011.02.083]

86 **Aryaie AH**, Singer JL, Fayezizadeh M, Lash J, Marks JM. Efficacy of endoscopic management of leak after foregut surgery with endoscopic covered self-expanding metal stents (SEMS). *Surg Endosc* 2017; **31**: 612-617 [PMID: 27317034 DOI: 10.1007/s00464-016-5005-8]

87 **do Monte Junior ES**, de Moura DTH, Ribeiro IB, Hathorn KE, Farias GFA, Turiani CV, Medeiros FS, Bernardo WM, de Moura EGH. Endoscopic vacuum therapy versus endoscopic stenting for upper gastrointestinal transmural defects: Systematic review and meta-analysis. *Dig Endosc* 2021; **33**: 892-902 [PMID: 33300634 DOI: 10.1111/den.13813]

88 **Rausa E**, Asti E, Aiolfi A, Bianco F, Bonitta G, Bonavina L. Comparison of endoscopic vacuum therapy versus endoscopic stenting for esophageal leaks: systematic review and meta-analysis. *Dis Esophagus* 2018; **31** [PMID: 29939229 DOI: 10.1093/dote/doy060]

89 **Archid R**, Bazerbachi F, Abu Dayyeh BK, Hönes F, Ahmad SJS, Thiel K, Nadiradze G, Königsrainer A, Wichmann D. Endoscopic Negative Pressure Therapy (ENPT) Is Superior to Stent Therapy for Staple Line Leak After Sleeve Gastrectomy: a Single-Center Cohort Study. *Obes Surg* 2021; **31**: 2511-2519 [PMID: 33650088 DOI: 10.1007/s11695-021-05287-z]

90 **Schniewind B**, Schafmayer C, Voehrs G, Egberts J, von Schoenfels W, Rose T, Kurdow R, Arlt A, Ellrichmann M, Jürgensen C, Schreiber S, Becker T, Hampe J. Endoscopic endoluminal vacuum therapy is superior to other regimens in managing anastomotic leakage after esophagectomy: a comparative retrospective study. *Surg Endosc* 2013; **27**: 3883-3890 [PMID: 23708716 DOI: 10.1007/s00464-013-2998-0]

91 **Berlth F**, Bludau M, Plum PS, Herbold T, Christ H, Alakus H, Kleinert R, Bruns CJ, Hölscher AH, Chon SH. Self-Expanding Metal Stents Versus Endoscopic Vacuum Therapy in Anastomotic Leak Treatment After Oncologic Gastroesophageal Surgery. *J Gastrointest Surg* 2019; **23**: 67-75 [PMID: 30374816 DOI: 10.1007/s11605-018-4000-x]

92 **Tachezy M**, Chon SH, Rieck I, Kantowski M, Christ H, Karstens K, Gebauer F, Goeser T, Rösch T, Izbicki JR, Bruns CJ. Endoscopic vacuum therapy versus stent treatment of esophageal anastomotic leaks (ESOLEAK): study protocol for a prospective randomized phase 2 trial. *Trials* 2021; **22**: 377 [PMID: 34078426 DOI: 10.1186/s13063-021-05315-4]

93 **Gubler C**, Vetter D, Schmidt HM, Müller PC, Morell B, Raptis D, Gutschow CA. Preemptive endoluminal vacuum therapy to reduce anastomotic leakage after esophagectomy: a game-changing approach? *Dis Esophagus* 2019; **32** [PMID: 30596963 DOI: 10.1093/dote/doy126]

94 **Neumann PA**, Mennigen R, Palmes D, Senninger N, Vowinkel T, Laukoetter MG. Pre-emptive endoscopic vacuum therapy for treatment of anastomotic ischemia after esophageal resections. *Endoscopy* 2017; **49**: 498-503 [PMID: 28107761 DOI: 10.1055/s-0042-123188]

95 **Müller PC**, Morell B, Vetter D, Raptis DA, Kapp JR, Gubler C, Gutschow CA. Preemptive Endoluminal Vacuum Therapy to Reduce Morbidity After Minimally Invasive Ivor Lewis Esophagectomy: Including a Novel Grading System for Postoperative Endoscopic Assessment of GI-Anastomoses. *Ann Surg* 2021; **274**: 751-757 [PMID: 34334639 DOI:

10.1097/SLA.0000000000005125]

96 **Yasuda JL**, Svetanoff WJ, Staffa SJ, Zendejas B, Hamilton TE, Jennings RW, Ngo PD, Jason Smithers C, Manfredi MA. Prophylactic negative vacuum therapy of high-risk esophageal anastomoses in pediatric patients. *J Pediatr Surg* 2021; **56**: 944-950 [PMID: 33342604 DOI: 10.1016/j.jpedsurg.2020.12.002]

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2023 June 16; 15(6): 434-439

DOI: 10.4253/wjge.v15.i6.434

ISSN 1948-5190 (online)

MINIREVIEWS

Flexible robotic endoscopy for treating gastrointestinal neoplasms

Keiichiro Kume

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ohki T, Japan

Received: December 21, 2022
Peer-review started: December 21, 2022
First decision: April 13, 2023
Revised: April 14, 2023
Accepted: May 4, 2023
Article in press: May 4, 2023
Published online: June 16, 2023

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Abstract

Therapeutic flexible endoscopic robotic systems have been developed primarily as a platform for endoscopic submucosal dissection (ESD) in the treatment of early-stage gastrointestinal cancer. Since ESD can only be performed by highly skilled endoscopists, the goal is to lower the technical hurdles to ESD by introducing a robot. In some cases, such robots have already been used clinically, but they are still in the research and development stage. This paper outlined the current status of development, including a system by the author's group, and discussed future challenges.

Key Words: Therapeutic flexible endoscopic robotic systems; Endoscopic submucosal dissection; Tissue triangulation

Core Tip: The current status and future issues in the new standardization that therapeutic flexible endoscopic robotic systems have brought to endoscopic submucosal dissection and endoscopic full-thickness resection were outlined.

Citation: Kume K. Flexible robotic endoscopy for treating gastrointestinal neoplasms. *World J Gastrointest Endosc* 2023; 15(6): 434-439
URL: https://www.wjgnet.com/1948-5190/full/v15/i6/434.htm
DOI: https://dx.doi.org/10.4253/wjge.v15.i6.434

INTRODUCTION

Therapeutic flexible endoscopic robotic systems were initially developed as a platform for natural orifice transluminal endoscopic surgery (NOTES)[1,2]. However, NOTES was not widely adopted as a treatment modality, and development shifted to

endoscopic submucosal dissection (ESD), a highly complex, gastrointestinal endoscopic procedure that emerged as a treatment modality for early-stage gastrointestinal cancer. The author's group has also developed a robotic system for ESD known as the Endoscopic Therapeutic Robot System (ETRS)[3]. Various reviews have been published on this subject[4-7]. This paper provided an overview from a developer's perspective of the current status and future issues in the development of a therapeutic flexible endoscopic robot that can be adapted to ESD and to next-generation endoscopic full-thickness resection (EFTR) therapy.

INTRODUCTION TO ROBOTICS IN ESD

ESD is a treatment modality that uses an electronic knife *via* the forceps channel of a flexible endoscope. First, an incision is made around the lesion (*e.g.*, early-stage cancer) at submucosal depth, and then the lesion is dissected from the wall of the digestive tract at the submucosal layer[8,9]. ESD allows en bloc resection of large lesions, which could not be performed with the conventional endoscopic mucosal resection modality. However, the procedure is very difficult and time-consuming because incision and dissection are performed by counter traction, which was achieved only by manual manipulation of the angle and axis of a single flexible endoscope.

This was an opportunity for the introduction of robotics. ENDOSAMURAI was developed for use with NOTES[10]. The system is equipped with two arm forceps that resemble hands at the tip of a flexible endoscope, with grasping forceps serving as the left hand and knife forceps as the right hand. Each element of the procedure, such as incision, dissection, and hemostasis, is intuitively performed by grasping and pulling with precise tissue triangulation[11]. The arrival of ENDOSAMURAI marked the beginning of the development of a therapeutic flexible endoscopic robot for performing ESD and EFTR [11]. Specifically, the shift from counter traction with a single flexible endoscope to tissue triangulation with two robotic arm forceps was a major contribution of robotics to ESD and other highly challenging endoscopic procedures.

A THERAPEUTIC FLEXIBLE ENDOSCOPIC ROBOT FOR PERFORMING ESD AND EFTR

In this section, systems that achieve tissue triangulation with multi-degrees-of-freedom (multi-DOF) robotic forceps and have been implemented for ESD and EFTR in animals or animal organs were reviewed along with a discussion of the clinical application of some systems.

Master and slave transluminal endoscopic robot

Master and slave transluminal endoscopic robot (MASTER) (Endomaster Pte Ltd., Singapore, Singapore) was developed primarily by the University of Singapore and was the first robot to clinically implement ESD for early-stage gastric cancer[12-14]. Grasping forceps and knife forceps with 7 DOF were mounted in the two forceps channels of an Olympus GIF-2T240 endoscope, and they could be manipulated by computer control using a dedicated master device. Submucosal dissection was made possible by good tissue triangulation, but other procedures such as marking and peripheral incision were performed separately using a conventional flexible endoscope, which necessitated repeated replacement of the flexible endoscope. The system also required another endoscopist to operate the flexible endoscope itself. This system has been implemented for EFTR of the stomach using live pigs[15].

Endomaster endoluminal assistant for surgical endoscopy system

The fixed configuration of the two robotic forceps in the old MASTER system made it impossible to exchange forceps, whereas a notable improvement of the next-generation MASTER systems was that the two grasping and knife robotic forceps could now be inserted and removed. The dedicated flexible endoscope has three channels: Two for robotic forceps and one for surgical instruments. The addition of rotation, insertion, and removal capabilities to the operations of the robotic forceps themselves resulted in 9 DOF and made the system more intuitive and easier to operate[16]. This system was initially implemented in colorectal ESD using live cows and is now being applied in a clinical setting[17]. Insofar as the flexible endoscope itself is not robotically operated and requires another endoscopist, there are no major changes in this regard.

Endoluminal surgical system

The endoluminal surgical system (ColubrisMX, Inc., Houston, TX, United States) consists of a scope called a Colubriscope, robotic forceps inserted into the scope, and an operating console for the forceps [18,19]. The Colubriscope has an external diameter of 22 mm and four channels: Two for robotic forceps (one dedicated camera channel and one surgical instrument channel) and a separate dedicated channel for air supply and degassing. Unlike other robotic systems that have a camera function in the flexible endoscope itself, a single camera scope can be inserted into the Colubriscope's forceps channel, allowing

independent adjustment of the field of view. Another advanced feature is the use of robotic grasping forceps in the left hand to obtain good tissue triangulation while using built-in powered scissors in the robotic forceps of the right hand to perform incision and dissection by means of hot dissection. This feature also has the potential for use in procedures other than ESD. This system is also noteworthy in that it allows suture manipulation using both left and right robotic grasping forceps, and it is capable of EFTR. ESD and postresection suturing were performed 20 times using porcine colons[18].

Flex robotic system

The Flex Robotic System (Medrobotics Corporation, Raynham, MA, United States) is a master-slave robotic system approved by the United States Food and Drug Administration in 2017 as a robotic system for head and neck surgery[20,21]. This perfected system has two forceps channels (left and right) on the outside of the flexible endoscope, through which dedicated forceps are inserted to allow two-handed operation. Two forceps can be selected from several types, such as grasping, electric scalpel, and powered scissors, to perform incision, dissection, resection, suturing, and so forth. The flexible endoscope itself can also be remotely operated, allowing almost all operations to be performed by a single endoscopist sitting at a dedicated console. The implementation of ESD in the bovine colon has shown that even a surgeon inexperienced in ESD can easily master this technique[20]. However, because this system is designed for head and neck surgery, the external diameter of the flexible endoscope is too large for insertion into the upper gastrointestinal tract, and with a length of 25 cm, it cannot be used for deep lesions in the colon.

Endoluminal assistant for surgical endoscopy

The Endoluminal Assistant for Surgical Endoscopy (ICube Laboratory, Strasbourg, France) is a master-slave robotic system developed as a successor to the ISIS-Scope/STRAS system (Karl Storz, IRCAD, Tuttlingen, Germany)[22,23]. It has two channels for robotic forceps and a channel for conventional surgical instruments, and through robotic control of the grasping and knife forceps, it can be used to perform mucous membrane incision and submucosal dissection with precise tissue triangulation. Submucosal local injection is also possible by inserting a syringe needle through the channel for conventional surgical instruments. The flexible endoscope itself can also be operated by a joystick, allowing almost all procedures to be performed by a single endoscopist sitting at a dedicated console. ESD of the colon has been achieved in live pigs[23].

ETRS

The ETRS (Figure 1) is a master-slave robotic system developed by the author's group exclusively for ESD[3]. We started by developing a platform to remotely control movements of the endoscope itself, which we named the Endoscopic Operation Robot (EOR)[24]. The current third-generation EOR is equipped with two-way haptic feedback functions that provide haptic feedback (force sensation) *via* the master unit while transmitting a force equal to that applied by the operator on the master unit to the endoscope tip, and all scope operations can be performed with one hand[24]. We then developed a master-slave system capable of remotely operating three different endoscopic instruments (grasping forceps, knife forceps, and injection-needle catheters), and we combined this system with the improved EOR version 3 (Figure 2) to create a novel gastrointestinal endoscopic robot in which all operations are controlled remotely. All procedural elements required for ESD, such as incision, dissection, submucosal local injection, water jetting, air supply, aspiration, and lesion recovery, can be performed by a single endoscopist sitting at a console. ESD has been performed in a resected pig stomach[3].

FUTURE ISSUES

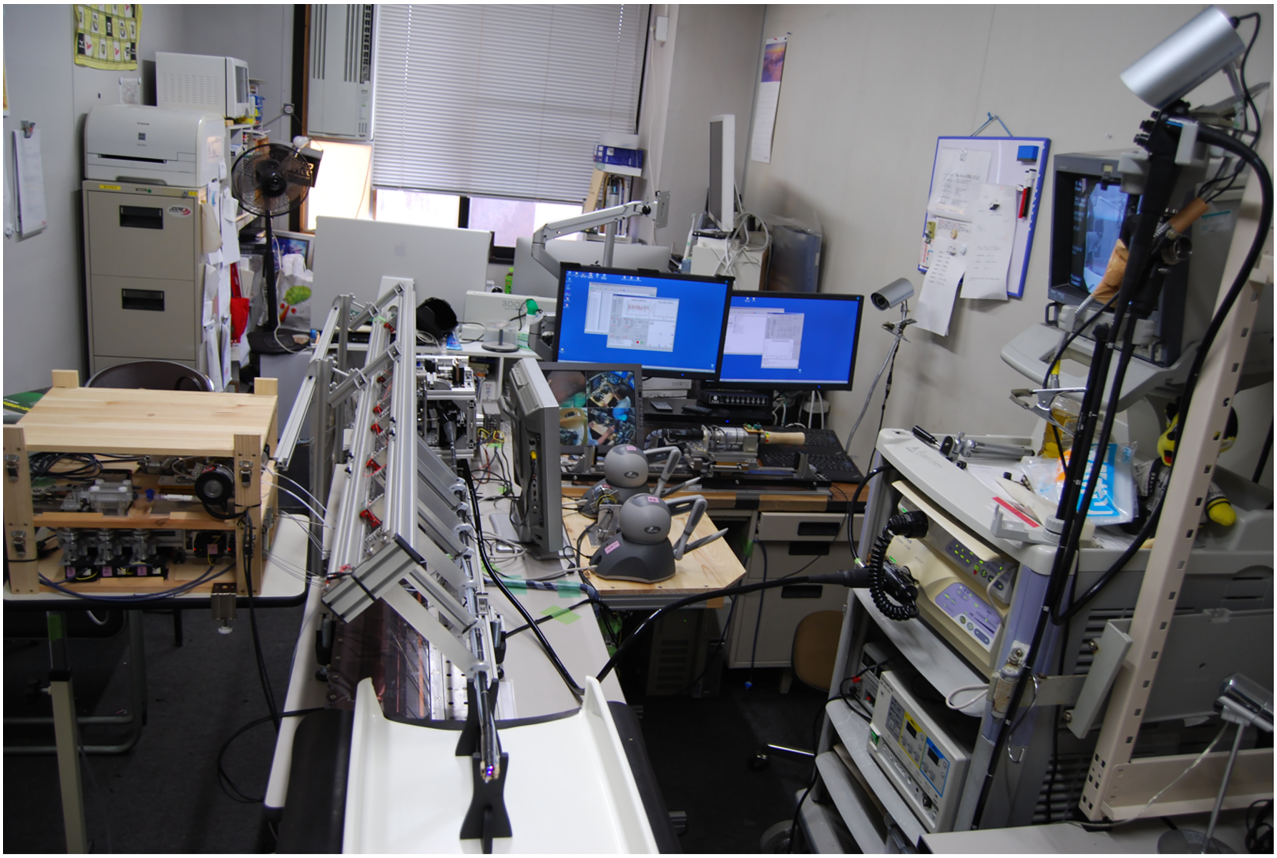
ESD is a procedure that can only be performed by highly skilled endoscopists, but therapeutic flexible endoscopic robotic systems allow less-experienced endoscopists to perform ESD by tissue triangulation using both hands to manipulate two multi-DOF robotic arm forceps. However, compared to the perfected surgical robots as exemplified by da Vinci, there are still many issues that need to be addressed at the research level before wider general clinical application.

Lesion access

For example, ESD is intended to treat lesions in the upper gastrointestinal tract as far as the duodenum and lesions in the lower gastrointestinal tract as far as the cecum. Each robotic system must be able to easily reach the lesion site so that it can adequately fulfill its potential. Current systems are still inadequate for accessing lesions, mainly because the scope cannot be operated over a sufficient length.

Versatility with cost-effectiveness

Dedicated ESD and EFTR robots are not cost-effective in terms of system scale because they tend to be large and complex. The Flex Robotic System was developed for head and neck surgery and has been



DOI: 10.4253/wjge.v15.i6.434

Figure 1 Endoscopic therapeutic robot system.

applied to colorectal ESD, but this system should be further developed so that it can be adapted to other diseases. Many of the systems introduced allow the replacement of robotic forceps. However, by expanding the robotic forceps options and forceps channels so that complex sutures and anastomoses can be performed at will, there is also room for development that extends the application of these systems to areas where flexible endoscopes are superior to rigid endoscopes, such as thoracic and intra-abdominal surgery. Nevertheless, all procedures must be performed within the caliber of a gastrointestinal endoscope, and greater development within these fine size constraints is needed.

Arrangement of operators

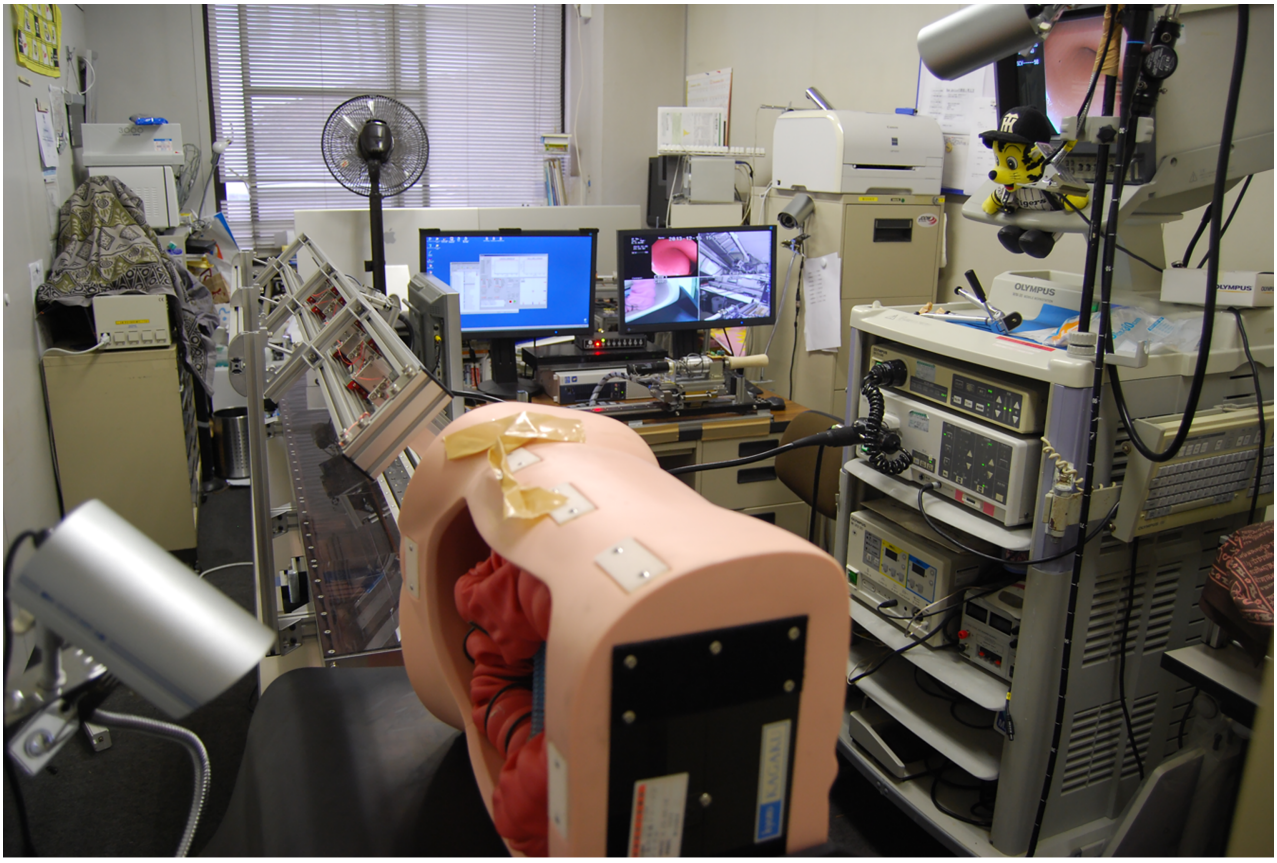
The ETRS developed by the author's group enables a single endoscopist sitting at a console to perform all the procedures required for ESD, although the system still has many other issues. Many current flexible endoscopes require assistants for their operation, and when complex, coordinated operation by two or more operators is needed, the hurdle for standardized operations becomes high. In the author's opinion, assistants should perform only the minimum necessary operations, such as changing forceps, and a single endoscopist should be able to perform as much of the surgery as possible.

Developing autonomy

The purpose of the surgical robotic systems currently used clinically is to provide operational support to surgeons and not to operate autonomously. If a robot were to be perfected as an operational support robot, it could be implemented clinically. For example, the smart tissue autonomous robot, which was developed as an autonomous surgical robot, is already performing automated intestinal anastomosis in live pigs[25]. Autonomous support was introduced into surgical robotic systems along with the establishment of phased objectives that must be met, in the same way that levels have been set for automated driving in automobiles[26]. This should begin with autonomous optimization of the surgical field so that the surgeon can always operate under an optimal surgical field.

CONCLUSION

Therapeutic flexible endoscopic robotic systems are being developed for ESD and EFTR. While some have been used clinically, most systems remain in the research and development stage. These robotic



DOI: 10.4253/wjge.v15.i6.434

Figure 2 Endoscopic operation robot version 3.

systems are expected to offer numerous advantages to surgeons, but a number of issues will need to be addressed before there is widespread application in clinical settings.

FOOTNOTES

Author contributions: Kume K conceived of, designed, prepared and wrote this review.

Supported by Grant-in-Aid for Scientific Research (KAKENHI), No. 23500573, No. 263500554, No. 17K01431 and No. 20K12700; Grant of the Princess Takamatsu Cancer Research Fund, No. 13-24505; and Terumo Life Science Foundation, No. 15-I101 and No. 20-III119.

Conflict-of-interest statement: Dr. Kume reports grants from Grant-in-Aid for Scientific Research, grants from Grant of the Princess Takamatsu Cancer Research Fund, grants from Terumo Foundation for Life and Arts, during the conduct of the study; In addition, Dr. Kume has a patent in Japan. No. 5605613 issued, and a patent in Japan No. 5880952 was issued.

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S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Cai YX

REFERENCES

1 **Swanstrom LL**. NOTES: Platform development for a paradigm shift in flexible endoscopy. *Gastroenterology* 2011; **140**: 1150-1154.e1 [PMID: 21334331 DOI: 10.1053/j.gastro.2011.02.031]

2 **Yeung BP**, Gourlay T. A technical review of flexible endoscopic multitasking platforms. *Int J Surg* 2012; **10**: 345-354 [PMID: 22641123 DOI: 10.1016/j.ijsu.2012.05.009]

3 **Kume K**, Sakai N, Ueda T. Development of a Novel Gastrointestinal Endoscopic Robot Enabling Complete Remote Control of All Operations: Endoscopic Therapeutic Robot System (ETRS). *Gastroenterol Res Pract* 2019; **2019**: 6909547 [PMID: 31781197 DOI: 10.1155/2019/6909547]

4 **Cui Y**, Thompson CC, Chiu PWY, Gross SA. Robotics in therapeutic endoscopy (with video). *Gastrointest Endosc* 2022; **96**: 402-410 [PMID: 35667390 DOI: 10.1016/j.gie.2022.05.019]

5 **Marlicz W**, Ren X, Robertson A, Skonieczna-Żydecka K, Łoniewski I, Dario P, Wang S, Plevris JN, Koulaouzidis A, Ciuti G. Frontiers of Robotic Gastroscopy: A Comprehensive Review of Robotic Gastroscopes and Technologies. *Cancers (Basel)* 2020; **12** [PMID: 32998213 DOI: 10.3390/cancers12102775]

6 **Saito Y**, Sumiyama K, Chiu PW. Robot assisted tumor resection devices. *Expert Rev Med Devices* 2017; **14**: 657-662 [PMID: 28726517 DOI: 10.1080/17434440.2017.1358087]

7 **Yeung BP**, Chiu PW. Application of robotics in gastrointestinal endoscopy: A review. *World J Gastroenterol* 2016; **22**: 1811-1825 [PMID: 26855540 DOI: 10.3748/wjg.v22.i5.1811]

8 **Ono H**, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, Hosokawa K, Shimoda T, Yoshida S. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001; **48**: 225-229 [PMID: 11156645 DOI: 10.1136/gut.48.2.225]

9 **Oka S**, Tanaka S, Kaneko I, Mouri R, Hirata M, Kawamura T, Yoshihara M, Chayama K. Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. *Gastrointest Endosc* 2006; **64**: 877-883 [PMID: 17140890 DOI: 10.1016/j.gie.2006.03.932]

10 **Spaun GO**, Zheng B, Swanström LL. A multitasking platform for natural orifice translumenal endoscopic surgery (NOTES): a benchtop comparison of a new device for flexible endoscopic surgery and a standard dual-channel endoscope. *Surg Endosc* 2009; **23**: 2720-2727 [PMID: 19360364 DOI: 10.1007/s00464-009-0476-5]

11 **Ikeda K**, Sumiyama K, Tajiri H, Yasuda K, Kitano S. Evaluation of a new multitasking platform for endoscopic full-thickness resection. *Gastrointest Endosc* 2011; **73**: 117-122 [PMID: 21074762 DOI: 10.1016/j.gie.2010.09.016]

12 **Ho KY**, Phee SJ, Shabbir A, Low SC, Huynh VA, Kencana AP, Yang K, Lomanto D, So BY, Wong YY, Chung SC. Endoscopic submucosal dissection of gastric lesions by using a Master and Slave Transluminal Endoscopic Robot (MASTER). *Gastrointest Endosc* 2010; **72**: 593-599 [PMID: 20646698 DOI: 10.1016/j.gie.2010.04.009]

13 **Wang Z**, Phee SJ, Lomanto D, Goel R, Rebala P, Sun ZL, Trasti S, Reddy N, Wong JY, Ho KY. Endoscopic submucosal dissection of gastric lesions by using a master and slave transluminal endoscopic robot: an animal survival study. *Endoscopy* 2012; **44**: 690-694 [PMID: 22723184 DOI: 10.1055/s-0032-1309404]

14 **Phee SJ**, Reddy N, Chiu PW, Rebala P, Rao GV, Wang Z, Sun Z, Wong JY, Ho KY. Robot-assisted endoscopic submucosal dissection is effective in treating patients with early-stage gastric neoplasia. *Clin Gastroenterol Hepatol* 2012; **10**: 1117-1121 [PMID: 22642951 DOI: 10.1016/j.cgh.2012.05.019]

15 **Chiu PW**, Phee SJ, Wang Z, Sun Z, Poon CC, Yamamoto T, Penny I, Wong JY, Lau JY, Ho KY. Feasibility of full-thickness gastric resection using master and slave transluminal endoscopic robot and closure by Overstitch: a preclinical study. *Surg Endosc* 2014; **28**: 319-324 [PMID: 23990156 DOI: 10.1007/s00464-013-3149-3]

16 **Chiu PWY**, Ho KY, Phee SJ. Colonic endoscopic submucosal dissection using a novel robotic system (with video). *Gastrointest Endosc* 2021; **93**: 1172-1177 [PMID: 32991869 DOI: 10.1016/j.gie.2020.09.042]

17 **Chiu PW**. ESD of rectal lesion by EndoMASTER EASE system. Endo Swiss Channel. Available from: https://www.youtube.com/watch?v=g2huLJEfDZ4&t=388s

18 **Atallah S**, Sanchez A, Bianchi E, Larach SW. Envisioning the future of colorectal surgery: preclinical assessment and detailed description of an endoluminal robotic system (ColubrisMX ELS). *Tech Coloproctol* 2021; **25**: 1199-1207 [PMID: 34224035 DOI: 10.1007/s10151-021-02481-0]

19 **Robotic Surgery Academy**. Colobris MX. Available from: https://www.youtube.com/watch?v=in_IuQiAZg8&t=500s

20 **Turiani Hourneaux de Moura D**, Aihara H, Jirapinyo P, Farias G, Hathorn KE, Bazarbashi A, Sachdev A, Thompson CC. Robot-assisted endoscopic submucosal dissection versus conventional ESD for colorectal lesions: outcomes of a randomized pilot study in endoscopists without prior ESD experience (with video). *Gastrointest Endosc* 2019; **90**: 290-298 [PMID: 30922861 DOI: 10.1016/j.gie.2019.03.016]

21 **Moura DTH**, Aihara H, Thompson CC. Robotic-assisted surgical endoscopy: a new era for endoluminal therapies. *VideoGIE* 2019; **4**: 399-402 [PMID: 31517160 DOI: 10.1016/j.vgie.2019.04.014]

22 **Zorn L**, Nageotte F, Zanne P, Legner A, Dallemagne B, Marescaux J, de Mathelin M. A Novel Telemanipulated Robotic Assistant for Surgical Endoscopy: Preclinical Application to ESD. *IEEE Trans Biomed Eng* 2018; **65**: 797-808 [PMID: 28678698 DOI: 10.1109/TBME.2017.2720739]

23 **Mascagni P**, Lim SG, Fiorillo C, Zanne P, Nageotte F, Zorn L, Perretta S, de Mathelin M, Marescaux J, Dallemagne B. Democratizing Endoscopic Submucosal Dissection: Single-Operator Fully Robotic Colorectal Endoscopic Submucosal Dissection in a Pig Model. *Gastroenterology* 2019; **156**: 1569-1571.e2 [PMID: 30768985 DOI: 10.1053/j.gastro.2018.12.046]

24 **Kume K**, Sakai N, Goto T. Development of a novel endoscopic manipulation system: the Endoscopic Operation Robot ver.3. *Endoscopy* 2015; **47**: 815-819 [PMID: 25910062 DOI: 10.1055/s-0034-1391973]

25 **Saeidi H**, Opfermann JD, Kam M, Wei S, Leonard S, Hsieh MH, Kang JU, Krieger A. Autonomous robotic laparoscopic surgery for intestinal anastomosis. *Sci Robot* 2022; **7**: eabj2908 [PMID: 35080901 DOI: 10.1126/scirobotics.abj2908]

26 **Haidegger T**. Autonomy for surgical robots: Concepts and paradigms. *IEEE Trans Med Robot Bionics* 2019; **1**: 65-76 [DOI: 10.1109/TMRB.2019.2913282]

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2023 June 16; 15(6): 440-446

DOI: 10.4253/wjge.v15.i6.440

ISSN 1948-5190 (online)

MINIREVIEWS

Endoscopic intraductal radiofrequency ablation for extrahepatic cholangiocarcinoma: An update (2023)

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Bredt LC, Brazil; Ricci AD, Italy

Received: December 27, 2022
Peer-review started: December 27, 2022
First decision: January 17, 2023
Revised: February 15, 2023
Accepted: May 12, 2023
Article in press: May 12, 2023
Published online: June 16, 2023

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Abstract

Recently, endoscopic intraductal radiofrequency ablation (ID-RFA) has attracted attention as a local treatment method for malignant biliary obstruction (MBO). ID-RFA causes coagulative necrosis of the tumor tissue in the stricture and induces exfoliation. Its effects are expected to extend the patency period of biliary stents and prolong the survival period. Evidence for extrahepatic cholangiocarcinoma (eCCA) is gradually accumulating, and some reports show significant therapeutic effects in eCCA patients without distant metastasis. However, it is still far from an established treatment technique, and many unsolved problems remain. Therefore, when performing ID-RFA in clinical practice, it is necessary to understand and grasp the current evidence well and to operate appropriately for the true benefit of the patients. This paper reviews the current status, issues, and prospects of endoscopic ID-RFA for MBO, especially for eCCA.

Key Words: Intraductal radiofrequency ablation; Cholangiocarcinoma; Biliary tract; Stents; Endoscopy

Core Tip: Intraductal radiofrequency ablation can be a useful option as a local therapy for malignant biliary obstruction, but there are still many unclear points. Although increasing reports suggest its usefulness, mainly for extrahepatic cholangiocarcinoma without distant metastasis, it is still far from being a standard treatment. Additionally, it should be recognized that the currently available ablation catheter could not always provide sufficient ablation in all cases. In addition to accumulating further evidence, it is necessary to establish its usefulness, clarify its indication, and develop an innovative device that can perform appropriate ablation for all lesions.

Citation: Inoue T, Yoneda M. Endoscopic intraductal radiofrequency ablation for extrahepatic cholangiocarcinoma: An update (2023). *World J Gastrointest Endosc* 2023; 15(6): 440-446
URL: https://www.wjgnet.com/1948-5190/full/v15/i6/440.htm
DOI: https://dx.doi.org/10.4253/wjge.v15.i6.440

INTRODUCTION

Biliary drainage is an indispensable therapeutic technique for treating obstructive jaundice and cholangitis associated with malignant biliary obstruction (MBO). The endoscopic placement of a biliary stent was introduced in the 1980s[1]; owing to its minimal invasiveness and usefulness, it is now the procedure of choice in most cases of MBO. Although there are various types of stents, metal stents (MS) are recommended for unresectable cases because they have a longer patency period than plastic stents (PS)[2]. However, progress in antitumor therapy has resulted in extended survival period of malignant disease with MBO[3,4], and stent occlusion occurs in a relatively large number of cases even when MS is indwelled. Therefore, extending the stent's patency period is required, including changing the drainage strategy.

Against this background, intraductal radiofrequency ablation (ID-RFA) has emerged as a novel local treatment for MBO[5,6]. ID-RFA was introduced to prolong the patency of the stents. Besides, it has been suggested that it is effective in prolonging survival for extrahepatic cholangiocarcinoma (eCCA). Since the prognosis of eCCA is poor and numerous patients are unresectable at the time of diagnosis, ID-RFA has attracted huge attention and has high expectations as a feasible alternative. However, it is difficult to say that ID-RFA has been established because many unsolved problems remain. To effectively benefit patients, ID-RFA in clinical practice requires a thorough understanding of the available evidence and proper operation.

In this paper, we review the current status, issues, and prospects of endoscopic ID-RFA for MBO, particularly for eCCA.

EFFECT OF ID-RFA ON PROLONGING SURVIVAL FOR eCCA

It is considered that ID-RFA can extend the survival period by reducing the tumor burden, a secondary effect by prolonging the patency of the stent, and antitumor immunity[7,8]. Presently, five randomized controlled trials (RCTs)[9-13] of endoscopic ID-RFA have been reported (Table 1). Yang *et al*[9] and Gao *et al*[11] focus on only eCCA patients, while others involve patients with various diseases. The three RCTs with various etiology did not show a survival benefit of ID-RFA, while Yang *et al*[9] showed that the overall mean survival time was significantly longer in the ID-RFA with stent group (13.2 ± 0.6 *vs* 8.3 ± 0.5 mo; $P < 0.001$) and Gao *et al*[11] reported that the median overall survival was significantly higher in the patients receiving ID-RFA (14.3 *vs* 9.2 mo; hazard ratio, 0.488; 95% confidence interval, 0.351–0.678; $P < 0.001$). However, caution in interpreting these results is that both studies by Yang *et al*[9] and Gao *et al*[11] included a mixture of locally advanced and distant metastatic diseases, which were not investigated separately. Although there is hope for the abscopal effect, it is questionable whether ID-RFA, which only ablate the bile duct and its surroundings, has the same effect in patients with a distant metastatic lesion that are directly related to life prognosis and those with only locally advanced disease. Xia *et al*[14] reported a retrospective study with many cases of MBO because of various primary diseases and underwent ID-RFA, and stated that the effect of prolonged survival was shown only in eCCA without distant metastasis.

In summarizing the results of the study above, it is said that the effect of ID-RFA on prolonging the survival period for eCCA can be expected; however, that effect may be limited to locally advanced cases. Therefore, in the future, it will be necessary to further examine the relationship between each disease stage and the effectiveness of ID-RFA, especially focusing on the presence or absence of distant metastasis.

COMBINATION OF ID-RFA AND CHEMOTHERAPY FOR eCCA

Chemotherapy is the current standard treatment for unresectable eCCA[15]. However, the previous RCT by Yang *et al*[9] excluded patients who underwent chemotherapy, and the study by Gao *et al*[11] included only a minimal number of patients who underwent chemotherapy. Therefore, when performing ID-RFA in clinical practice, it is necessary to grasp another evidence of ID-RFA when combined with chemotherapy.

Table 1 Randomized controlled trials of endoscopic intraductal radiofrequency ablation for malignant biliary obstruction

Ref.	No. of patients		Etiology	Location	ID-RFA catheter	ID-RFA setting	Stent type	No. of ID-RFA applications	Stent patency period (median/mean)			Survival period (median/mean)			Adverse event rate		
	RFA + stent	Stent							ID-RFA + stent	Stent	*P* value	ID-RFA + stent	Stent	*P* value	ID-RFA + stent	Stent	*P* value
Yang *et al* [9], 2018	32	33	Cholangiocarcinoma	Distal, hilar	Habib	7-10W; 90s	PS	Every 3 m[a]	6.8 m[b]	3.4 m[b]	0.02	13.2 m	8.3 m	< 0.001	6.3%	9.1%	0.67
Kang *et al* [10], 2021[c]	24	24	Cholangiocarcinoma, pancreatic cancer, other	Distal, Hilar	ELRA	7W/10W; 120s; 80°C	UMS	1	132 d	116 d	0.440	244 m	180 m	0.281	4.2%	12.5%	0.609
Gao *et al* [11], 2021	87	87	Cholangiocarcinom[e]	Distal, hilar	Habib	7-10W; 90s	PS	2	3.7 m	4.1 m	0.674	14.3 m	9.2 m	< 0.001	27.6% (early event)	19.5% (early event)	0.211
Kang *et al* [12], 2022	15	15	Cholangiocarcinoma, gallbladder cancer	Hilar	ELRA	7W; 60-120s; 80°C	UMS	1-2	178 d	122 d	0.154	230 d	144 d	0.643	NA	NA	NS
Albers *et al* [13], 2022	42	44	Cholangiocarcinoma, pancreatic cancer, other	Distal, Hilar	Habib	10W; 90s	UMS	1	NA[d]	NA[d]	NA[d]	NA[d]	NA[d]	NA[d]	10.5%	2.3%	*P* = 0.18

[a]ID-RFA was repeated if the bile duct wall thickness was > 6 mm by intraductal ultrasonography every 3 mo.
[b]Stent replacement was performed every 3 mo even if it was not occluded.
[c]Cases of percutaneous approaches were also included.
[d]Cases of ampullary cancer were also included.
[e]Stent patency and overall survival rates after 3 and 6 mo did not differ significantly between groups.
ID-RFA: Intraductal radiofrequency ablation; PS: Plastic stent; UMS: Uncovered metal stent; NA: Not applicable; NS: Not significant.

There are three reports regarding the combination of chemotherapy and ID-RFA for eCCA[16-18] (Table 2). First, Yang *et al*[16] reported that the median overall survival was longer in patients who underwent ID-RFA and S-1 chemotherapy than in those who underwent only ID-RFA (16.0 *vs* 11.0 mo; $P < 0.001$), showing the additional effect of S-1 chemotherapy in patients who underwent ID-RFA. However, it noted that distant metastatic cases were excluded from this study. Second, Gonzalez-Carmona *et al*[17] conducted a retrospective study on the additional effect of ID-RFA on patients undergoing gemcitabine-based chemotherapy. They showed significantly longer median overall survival in patients with combined ID-RFA and chemotherapy compared to those with only chemotherapy (17.3 *vs* 8.6 mo, $P = 0.004$). On subgroup analysis of this study, longer median overall survival with the combination of ID-RFA and chemotherapy was maintained in patients with the non-metastatic disease (20.9 *vs* 12.4 mo, $P = 0.043$), whereas it disappeared in patients with metastatic disease (15.0 *vs* 8.6 mo, $P = 0.116$). Finally, Inoue *et al*[18] compared patients who underwent ID-RFA with gemcitabine and cisplatin chemotherapy and those with only gemcitabine and cisplatin chemotherapy. The median overall survival was significantly higher in the patients with ID-RFA and chemotherapy (17.1 *vs* 11.3 mo, $P = 0.017$), indicating an additional effect of ID-RFA in patients treated with

Table 2 Comparative studies of endoscopic intraductal radiofrequency ablation with chemotherapy for extrahepatic cholangiocarcinoma

Ref.	Treatment	No. of patients	Location	Metastatic, %	ID-RFA catheter	Stent type	No. of ID-RFA applications	Stent patency period (median)		Progression free survival (median)		Overall survival (median)	
Yang *et al*[16], 2020	S-1 chemotherapy + ID-RFA	37	Distal, Hilar	0	Habib	PS	3.3 (mean)	6.6 m	$P = 0.014$	12 m	$P < 0.001$	16.0 m	$P < 0.001$
	ID-RFA	38	Distal, Hilar	0	Habib	PS	2.4 (mean)	5.6 m		7 m		11.0 m	
Gonzalez-Carmona *et al*[17], 2022	GEM-based chemotherapy + ID-RFA	40	Distal, Hilar	37.5	Habib	PS	1-21	NA	NA	12.9 m	$P = 0.045$	17.3 m	$P = 0.004$
	GEM-based chemotherapy	26	Distal, Hilar	50.0	Habib	PS	-	NA		5.7 m		8.6 m	
Inoue *et al*[18], 2022	GEM with cisplatin + ID-RFA	25	Distal, Hilar	48	Habib	UMS	1.84 (mean)	10.7 m	$P = 0.048$	8.6 m	$P = 0.014$	17.1 m	$P = 0.017$
	GEM with cisplatin	25	Distal, Hilar	60	Habib	UMS	-	5.2 m		5.8 m		11.3 m	

ID-RFA: Intraductal radiofrequency ablation; PS: Plastic stent; GEM: Gemcitabine; NA: Not applicable; UMS: Uncovered metal stent.

gemcitabine and cisplatin. However, like the results of the study by Gonzalez-Carmona *et al*[17], subgroup analysis showed a significant difference in median overall survival in patients without distant metastases (23.1 *vs* 16.6 mo, $P = 0.032$), while no significant difference in patients with distant metastases (11.4 *vs* 8.5 mo, $P = 0.180$).

These results are similar to those reported by Xia *et al*[14]. The effect of ID-RFA, a local treatment, may be limited to locally advanced cases (no distant metastases). Systemic effects, including induction of antitumor immunity, need to be investigated in more detail, the including the mechanism and evidence from basic research.

EFFECT OF ID-RFA ON PROLONGING STENT PATENCY IN eCCA

In the two currently available RCT for eCCA, PS was used. Yang *et al*[9] showed that the mean stent patency was significantly longer in patients combined with ID-RFA (6.8 *vs* 3.4 mo, $P = 0.02$). In contrast, Gao *et al*[11] found that the median stent patency was insignificant with or without ID-RFA (3.7 *vs* 4.1, $P = 0.674$). However, in Yang *et al*'s study, stent replacement was performed every 3 mo, and interpretation is difficult because it was not a pure evaluation of stent patency[9]. The other RCTs, in which patients were not limited to eCCA, used uncovered MS[10,12,13]. They all showed no significant differences in stent patency with or without ID-RFA.

These results suggest that there is currently no strong evidence to support the effectiveness of endoscopic ID-RFA in prolonging stent patency. However, numerous studies, including prospective, retrospective, and percutaneous approaches, have shown that ID-RFA prolongs stent patency, especially when combined with uncovered MS[5,6,19-24]. Therefore, it may be considered promising that ID-RFA prolongs stent patency, but it is not easy to judge its usefulness because there is not enough evidence. In the future, it will be necessary to determine the usefulness of ID-RFA in further studies by strictly standardizing the target disease, the site of stricture, the type of stent to be used, the placement method, and the approach method.

FUTURE PROSPECTS OF ENDOSCOPIC ID-RFA

As previously indicated, a number of reports of ID-RFA in recent years and evidence has accumulated regarding its therapeutic efficacy, especially for eCCA without distant metastasis. However, while robust evidence is lacking, there are still many unresolved issues, such as differences in tumor localization between the hepatic hilum and distal bile duct, the number of ablation applications performed, and so on. Therefore, it is necessary to conduct well-designed clinical studies and further clarify the indications and situations in which ID-RFA is useful. Additionally, in treating hepatocellular carcinoma, it has been suggested that ablation induce systemic immune effects, so combined use with immunotherapy is expected to prolong further survival[25]. Since recent significant advances were made with immunotherapy in the first-line treatment of advanced CCA with the addition of durvalumab to cisplatin-gemcitabine chemotherapy showing a survival benefit[26,27], it is also expected to investigate the additional effect of combining with ID-RFA.

Another problem is that, sometimes, the currently available ID-RFA catheters cannot ablate sufficiently due to their structure[5,28], and it has been pointed out that the portion in contact with the electrode is ablated strongly, resulting in uneven and unstable ablation depth and area[29]. Additionally, it has been suggested that the entire lesion must appropriately ablate to improve stent patency and survival[12,28]. Therefore, to firmly determine the effect of the use of ID-RFA and for the spread of ID-RFA, improvement of the device is essential; the development of a device that can obtain a stable ablation effect in any stricture lesion and appropriately control the ablation range is needed. Although it is still in the animal experiment stage, attempts have also been made to develop a balloon-based ID-RFA catheter that enables regular contact all around[30,31]. This balloon ID-RFA catheter provides a significantly more stable and appropriate ablation range than the conventional ID-RFA catheter[29]. In addition, a system that can perform ablation under real-time observation with cholangioscopy has also appeared[32]. Next-generation ID-RFA devices are expected to enter clinical trials soon, resulting in enhanced treatment outcomes and broader ID-RFA indications.

CONCLUSION

The current issues and prospects of endoscopic ID-RFA were reviewed, focusing on eCCA. ID-RFA can be a useful option as an intrabiliary local therapy, but there are still many unclear points. Although increasing reports suggest its usefulness, mainly for eCCA without distant metastasis, it is still far from being a standard treatment. Additionally, it should be recognized that the existing catheter could not always provide sufficient ablation in all cases. Therefore, in addition to accumulating further evidence, it is necessary to establish its usefulness, clarify its indication, and develop an innovative device that can perform appropriate ablation for all lesions.

FOOTNOTES

Author contributions: Inoue T contributed to conception and design, data acquisition, analysis and interpretation, and drafting and revision of the manuscript; Yoneda M contributed to data interpretation, and revision of the manuscript.

Conflict-of-interest statement: Tadahisa Inoue received honoraria from Boston Scientific Japan and Japan Lifeline Co., Ltd. Masashi Yoneda discloses no financial relationships relevant to this publication.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Fan JR

REFERENCES

1 **Soehendra N**, Reynders-Frederix V. Palliative bile duct drainage - a new endoscopic method of introducing a transpapillary drain. *Endoscopy* 1980; **12**: 8-11 [PMID: 7353562 DOI: 10.1055/s-2007-1021702]
2 **Almadi MA**, Barkun A, Martel M. Plastic vs. Self-Expandable Metal Stents for Palliation in Malignant Biliary Obstruction: A Series of Meta-Analyses. *Am J Gastroenterol* 2017; **112**: 260-273 [PMID: 27845340 DOI: 10.1038/ajg.2016.512]
3 **Von Hoff DD**, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369**: 1691-1703 [PMID: 24131140 DOI: 10.1056/NEJMoa1304369]
4 **Valle J**, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J; ABC-02 Trial Investigators. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med* 2010; **362**: 1273-1281 [PMID: 20375404 DOI: 10.1056/NEJMoa0908721]
5 **Inoue T**, Yoneda M. Updated evidence on the clinical impact of endoscopic radiofrequency ablation in the treatment of malignant biliary obstruction. *Dig Endosc* 2022; **34**: 345-358 [PMID: 34107114 DOI: 10.1111/den.14059]
6 **Sofi AA**, Khan MA, Das A, Sachdev M, Khuder S, Nawras A, Lee W. Radiofrequency ablation combined with biliary stent placement versus stent placement alone for malignant biliary strictures: a systematic review and meta-analysis. *Gastrointest Endosc* 2018; **87**: 944-951.e1 [PMID: 29108980 DOI: 10.1016/j.gie.2017.10.029]
7 **Haen SP**, Pereira PL, Salih HR, Rammensee HG, Gouttefangeas C. More than just tumor destruction: immunomodulation by thermal ablation of cancer. *Clin Dev Immunol* 2011; **2011**: 160250 [PMID: 22242035 DOI: 10.1155/2011/160250]
8 **Giardino A**, Innamorati G, Ugel S, Perbellini O, Girelli R, Frigerio I, Regi P, Scopelliti F, Butturini G, Paiella S, Bacchion M, Bassi C. Immunomodulation after radiofrequency ablation of locally advanced pancreatic cancer by monitoring the immune response in 10 patients. *Pancreatology* 2017; **17**: 962-966 [PMID: 29037917 DOI: 10.1016/j.pan.2017.09.008]
9 **Yang J**, Wang J, Zhou H, Zhou Y, Wang Y, Jin H, Lou Q, Zhang X. Efficacy and safety of endoscopic radiofrequency ablation for unresectable extrahepatic cholangiocarcinoma: a randomized trial. *Endoscopy* 2018; **50**: 751-760 [PMID: 29342492 DOI: 10.1055/s-0043-124870]
10 **Kang H**, Chung MJ, Cho IR, Jo JH, Lee HS, Park JY, Park SW, Song SY, Bang S. Efficacy and safety of palliative endobiliary radiofrequency ablation using a novel temperature-controlled catheter for malignant biliary stricture: a single-center prospective randomized phase II TRIAL. *Surg Endosc* 2021; **35**: 63-73 [PMID: 32488654 DOI: 10.1007/s00464-020-07689-z]
11 **Gao DJ**, Yang JF, Ma SR, Wu J, Wang TT, Jin HB, Xia MX, Zhang YC, Shen HZ, Ye X, Zhang XF, Hu B. Endoscopic radiofrequency ablation plus plastic stent placement versus stent placement alone for unresectable extrahepatic biliary cancer: a multicenter randomized controlled trial. *Gastrointest Endosc* 2021; **94**: 91-100.e2 [PMID: 33359435 DOI: 10.1016/j.gie.2020.12.016]
12 **Kang H**, Han SY, Cho JH, Kim EJ, Kim DU, Yang JK, Jeon S, Park G, Lee TH. Efficacy and safety of temperature-controlled intraductal radiofrequency ablation in advanced malignant hilar biliary obstruction: A pilot multicenter randomized comparative trial. *J Hepatobiliary Pancreat Sci* 2022; **29**: 469-478 [PMID: 34800357 DOI: 10.1002/jhbp.1082]
13 **Albers D**, Schmidt A, Schiemer M, Caca K, Wannhoff A, Sauer P, Wiesweg M, Schumacher B, Dechene A. Impact of endobiliary radiofrequency ablation on biliary drainage in patients with malignant biliary strictures treated with uncovered self-expandable metal stents: a randomized controlled multicenter trial. *Gastrointest Endosc* 2022; **96**: 970-979 [PMID: 35667389 DOI: 10.1016/j.gie.2022.05.022]
14 **Xia MX**, Wang SP, Yuan JG, Gao DJ, Ye X, Wang TT, Wu J, Zhou DX, Hu B. Effect of endoscopic radiofrequency ablation on the survival of patients with inoperable malignant biliary strictures: A large cohort study. *J Hepatobiliary Pancreat Sci* 2022; **29**: 693-702 [PMID: 33829657 DOI: 10.1002/jhbp.960]
15 **Rizzo A**, Brandi G. First-line Chemotherapy in Advanced Biliary Tract Cancer Ten Years After the ABC-02 Trial: "And Yet It Moves!". *Cancer Treat Res Commun* 2021; **27**: 100335 [PMID: 33592561 DOI: 10.1016/j.ctarc.2021.100335]
16 **Yang J**, Wang J, Zhou H, Wang Y, Huang H, Jin H, Lou Q, Shah RJ, Zhang X. Endoscopic radiofrequency ablation plus a novel oral 5-fluorouracil compound versus radiofrequency ablation alone for unresectable extrahepatic cholangiocarcinoma. *Gastrointest Endosc* 2020; **92**: 1204-1212.e1 [PMID: 32437711 DOI: 10.1016/j.gie.2020.04.075]
17 **Gonzalez-Carmona MA**, Möhring C, Mahn R, Zhou T, Bartels A, Sadeghlar F, Bolch M, Vogt A, Kaczmarek DJ, Heling DJ, Dold L, Nattermann J, Branchi V, Matthaei H, Manekeller S, Kalff JC, Strassburg CP, Mohr RU, Weismüller TJ. Impact of regular additional endobiliary radiofrequency ablation on survival of patients with advanced extrahepatic cholangiocarcinoma under systemic chemotherapy. *Sci Rep* 2022; **12**: 1011 [PMID: 35046437 DOI: 10.1038/s41598-021-04297-2]
18 **Inoue T**, Naitoh I, Kitano R, Ibusuki M, Kobayashi Y, Sumida Y, Nakade Y, Ito K, Yoneda M. Endobiliary Radiofrequency Ablation Combined with Gemcitabine and Cisplatin in Patients with Unresectable Extrahepatic Cholangiocarcinoma. *Curr Oncol* 2022; **29**: 2240-2251 [PMID: 35448156 DOI: 10.3390/curroncol29040182]
19 **Li TF**, Huang GH, Li Z, Hao CF, Ren JZ, Duan XH, Zhang K, Chen C, Han XW, Jiao DC, Zhang MF, Wang YL.

Percutaneous transhepatic cholangiography and intraductal radiofrequency ablation combined with biliary stent placement for malignant biliary obstruction. *J Vasc Interv Radiol* 2015; **26**: 715-721 [PMID: 25817458 DOI: 10.1016/j.jvir.2015.01.037]

20 **Wang J**, Zhao L, Zhou C, Gao K, Huang Q, Wei B, Gao J. Percutaneous Intraductal Radiofrequency Ablation Combined with Biliary Stent Placement for Nonresectable Malignant Biliary Obstruction Improves Stent Patency but not Survival. *Medicine (Baltimore)* 2016; **95**: e3329 [PMID: 27082582 DOI: 10.1097/MD.0000000000003329]

21 **Wu TT**, Li WM, Li HC, Ao GK, Zheng F, Lin H. Percutaneous Intraductal Radiofrequency Ablation for Extrahepatic Distal Cholangiocarcinoma: A Method for Prolonging Stent Patency and Achieving Better Functional Status and Quality of Life. *Cardiovasc Intervent Radiol* 2017; **40**: 260-269 [PMID: 27743089 DOI: 10.1007/s00270-016-1483-2]

22 **Cui W**, Wang Y, Fan W, Lu M, Zhang Y, Yao W, Li J. Comparison of intraluminal radiofrequency ablation and stents vs. stents alone in the management of malignant biliary obstruction. *Int J Hyperthermia* 2017; **33**: 853-861 [PMID: 28540797 DOI: 10.1080/02656736.2017.1309580]

23 **Yu T**, Zhang W, Li C, Wang C, Gong G, Wang L, Li G, Chen Y, Wang X. Percutaneous intraductal radiofrequency ablation combined with biliary stent placement for treatment of malignant biliary obstruction. *Abdom Radiol (NY)* 2020; **45**: 3690-3697 [PMID: 32277241 DOI: 10.1007/s00261-020-02516-4]

24 **Uyanık SA**, Öğüşlü U, Çevik H, Atlı E, Yılmaz B, Gümüş B. Percutaneous endobiliary ablation of malignant biliary strictures with a novel temperature-controlled radiofrequency ablation device. *Diagn Interv Radiol* 2021; **27**: 102-108 [PMID: 33252335 DOI: 10.5152/dir.2020.20333]

25 **Chen S**, Zeng X, Su T, Xiao H, Lin M, Peng Z, Peng S, Kuang M. Combinatory local ablation and immunotherapies for hepatocellular carcinoma: Rationale, efficacy, and perspective. *Front Immunol* 2022; **13**: 1033000 [PMID: 36505437 DOI: 10.3389/fimmu.2022.1033000]

26 **Roth GS**, Neuzillet C, Sarabi M, Edeline J, Malka D, Lièvre A. Cholangiocarcinoma: what are the options in all comers and how has the advent of molecular profiling opened the way to personalised medicine? *Eur J Cancer* 2023; **179**: 1-14 [PMID: 36463640 DOI: 10.1016/j.ejca.2022.11.006]

27 **Rizzo A**, Ricci AD, Brandi G. Durvalumab: an investigational anti-PD-L1 antibody for the treatment of biliary tract cancer. *Expert Opin Investig Drugs* 2021; **30**: 343-350 [PMID: 33645367 DOI: 10.1080/13543784.2021.1897102]

28 **Inoue T**, Ibusuki M, Kitano R, Kobayashi Y, Ohashi T, Nakade Y, Sumida Y, Ito K, Yoneda M. Endobiliary radiofrequency ablation combined with bilateral metal stent placement for malignant hilar biliary obstruction. *Endoscopy* 2020; **52**: 595-599 [PMID: 32208498 DOI: 10.1055/a-1133-4448]

29 **Inoue T**, Ito K, Yoneda M. Novel balloon catheter-based endobiliary radiofrequency ablation system: Ex-vivo experimental study. *Dig Endosc* 2020; **32**: 974-978 [PMID: 31916300 DOI: 10.1111/den.13622]

30 **Inoue T**, Yoneda M. Evaluating the tissue effects of balloon-based endobiliary radiofrequency ablation in porcine bile ducts. *Int J Hyperthermia* 2020; **37**: 1383-1385 [PMID: 33327820 DOI: 10.1080/02656736.2020.1859627]

31 **Nociarova J**, Novak M, Polak J, Hrudka J, Porubsky S, Koc M, Rosina J, Grebenyuk AN, Sery R, Gurlich R, Hajer J. Development of Radiofrequency Ablation Generator and Balloon-Based Catheter for Microendoluminal Thin-Layer Ablation Therapy Using the Rat Duodenum as a Model of Low-Impedance Tissue. *J Healthc Eng* 2021; **2021**: 9986874 [PMID: 34603652 DOI: 10.1155/2021/9986874]

32 **Inoue T**, Kutsumi H, Ibusuki M, Yoneda M. Feasibility of balloon-based endobiliary radiofrequency ablation under cholangioscopy guidance in a swine model. *Sci Rep* 2021; **11**: 14254 [PMID: 34244576 DOI: 10.1038/s41598-021-93643-5]

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2023 June 16; 15(6): 447-457

DOI: 10.4253/wjge.v15.i6.447

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Role of endoscopic ultrasound for pre-intervention evaluation in early esophageal cancer

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Binda C, Italy; Edholm D, Sweden; Martino A, Italy

Received: February 24, 2023
Peer-review started: February 24, 2023
First decision: March 24, 2023
Revised: April 8, 2023
Accepted: May 12, 2023
Article in press: May 12, 2023
Published online: June 16, 2023

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Abstract

BACKGROUND

Endoscopic ultrasound (EUS) stands as an accurate imaging modality for esophageal cancer staging, however utilization of EUS in early-stage cancer management remains controversial. Identification of non-applicability of endoscopic interventions with deep muscular invasion with EUS in pre-intervention evaluation of early-stage esophageal cancer is compared to endoscopic and histologic indicators.

AIM

To display the role of EUS in pre-intervention early esophageal cancer staging and how the index endoscopic features of invasive esophageal malignancy compare for prediction of depth of invasion and cancer management.

METHODS

This was a retrospective study of patients who underwent pre-resection EUS after a diagnosis of esophageal cancer at a tertiary medical center from 2012 to 2022. Patient clinical data, initial esophagogastroduodenoscopy/biopsy, EUS, and final resection pathology reports were abstracted, and statistical analysis was conducted to assess the role of EUS in management decisions.

RESULTS

Forty nine patients were identified for this study. EUS T stage was concordant with histological T stage in 75.5% of patients. In determining submucosal involvement (T1a *vs* T1b), EUS had a specificity of 85.0%, sensitivity of 53.9%, and accuracy of 72.7%. Endoscopic features of tumor size > 2 cm and the presence of esophageal ulceration were significantly associated with deep invasion of cancer on histology. EUS affected management from endoscopic mucosal resecti-

on/submucosal dissection to esophagectomy in 23.5% of patients without esophageal ulceration and 6.9% of patients with tumor size < 2 cm. In patients without both endoscopic findings, EUS identified deeper cancer and changed management in 4.8% (1/20) of cases.

CONCLUSION

EUS was reasonably specific in ruling out submucosal invasion but had relatively poor sensitivity. Data validated endoscopic indicators suggested superficial cancers in the group with a tumor size < 2 cm and the lack of esophageal ulceration. In patients with these findings, EUS rarely identified a deep cancer that warranted a change in management.

Key Words: Endoscopic ultrasound; Esophageal early-stage cancer; Endoscopic intervention; Endoscopic indicators of invasive cancer; Cancer intervention; Endoscopy

Core Tip: This study aims to convey the role of endoscopic ultrasound (EUS) for early esophageal cancer considered for endoscopic or surgical resection and how the index endoscopic features of esophageal malignancy compare for prediction of depth of invasion and cancer management. This was a retrospective study of 49 patients who underwent pre-resection EUS after diagnosis of esophageal cancer. EUS was reasonably specific in ruling out submucosal invasion but had relatively poor sensitivity. Data validated endoscopic features suggesting superficial cancers including a tumor size < 2 cm and the lack of esophageal ulceration. In patients with these findings, EUS rarely identified a deep cancer that warranted a change in management.

Citation: Kahlon S, Aamar A, Butt Z, Urayama S. Role of endoscopic ultrasound for pre-intervention evaluation in early esophageal cancer. *World J Gastrointest Endosc* 2023; 15(6): 447-457
URL: https://www.wjgnet.com/1948-5190/full/v15/i6/447.htm
DOI: https://dx.doi.org/10.4253/wjge.v15.i6.447

INTRODUCTION

Esophageal cancer is the eighth-most common cancer and sixth-most common cause of mortality globally[1]. In the United States, an estimated 20,640 cases of esophageal cancer are diagnosed in 2022, and 16,410 deaths are expected from the disease, highlighting the importance of its diagnosis and treatment[2,3].

With the advent of less invasive interventions including endoscopic mucosal resection (EMR) or submucosal dissection (ESD) for superficial cancers, accurate clinical staging of esophageal cancer becomes critical in selecting appropriate treatment options[1]. Pre-intervention tumor depth staging (T staging) is vital in assessing which patients without an evidence of metastasis, would benefit from endoscopic or surgical intervention. Tumors limited to mucosa can be completely resected with endoscopic therapy due to lower risk of incomplete resection or lympho-vascular invasion[3]. NCCN guideline recommends endoscopic resection in the management of T1a lesions and superficial T1b lesions, or T1b-sm[1] lesions that superficially invade the submucosa[4]. Tumors staged T1b-sm[2] or sm[3] have significant risk for recurrence and warrant evaluation for esophagectomy[5].

Endoscopic ultrasound (EUS) has been commonly utilized as the most accurate imaging study for staging primary esophageal cancer in comparison to other modalities[4]. Specifically, EUS has been shown to accurately assess T staging in the cancer (73.2%-80.6%), excelling in distinguishing T3/T4 Lesions from T1/T2[6-9]. EUS remains a key component of locoregional assessment to determine the depth of invasion and nodal involvement while also allowing the possibility of fine-needle aspiration sampling[10]. Classifying more superficial lesions into T1a, T1b-sm[1], T1b-sm[2], or T1b-sm[3] lesions, however, has proven difficult *via* EUS[11]. Currently for superficial cancers, EUS is readily combined with EMR or ESD to optimize the clinical management. Specifically, EUS allows exclusion of the presence of a deeper cancer invasion, which makes an EMR or ESD potentially unsafe and/or lead to an incomplete intervention.

There are several studies delineating the correlation of endoscopic and biopsy assessments as evidence for deeper invasion in esophagus cancer in lieu of EUS[12-15]. These suggest that EUS may not provide additional information in situations where endoscopic or pathologic parameters sufficiently characterize esophageal cancers and fully dictate management. Thus, controversy remains in the utility of EUS in patients who have suspected early-stage esophageal cancer and how it can affect management. Current study aims to display the role of EUS for early esophageal cancer staging and

how the index endoscopic indicators of invasive esophageal malignancy compare for assessment of depth of invasion and the cancer management.

MATERIALS AND METHODS

Ethics

This was a retrospective study of patients who underwent pre-intervention EUS with a diagnosis of esophageal cancer between January 2012 to January 2022 at a tertiary medical center. This study period was used to minimize the effect of incomplete data allocation from the period prior to establishment of electronic medical record. This study was approved on November 1, 2021 by the Institutional Review Board of the hospital in accordance with its ethical standards and assigned IRB protocol number 1816393-1.

Study population

Ninety three patients were identified *via* EMR search conducted with assistance from the Clinical and Translational Science Center at University of California, Davis. The search was conducted at for patients with ICD-10 codes C15.0 to C15.9 logged for esophageal malignancies in their medical record and those with Current Procedural Terminology code 43242 logged for EUS procedures during the study period at our medical center. Patient's without electronic documentation of EUS procedure reports were excluded from the study. From this population, patients were ascertained who met the inclusion criteria of age over 18 years, established diagnosis from biopsies collected during index esophagogastroduodenoscopy (EGD), EUS conducted prior to any therapeutic intervention such as endoscopic/surgical resection. Exclusion criteria included: EUS was not conducted prior to any therapeutic interventions, EUS did not indicate staging, EUS did not yield a pathologic specimen, and patients treated with neoadjuvant treatment before esophagectomy. Forty nine patients met criteria for analysis. This is summarized in Figure 1.

T staging by EUS and pathologic diagnosis

EUS was performed with an Olympus radial echoendoscope (GF-UE160, Olympus America, Penn Valley, United States). EGD and EUS procedures were performed by a single endosonographer with over 10 years of experience at the beginning of the study period. Pre-operative T staging was made in accordance with TNM staging system for esophageal cancer with the 8th edition of the American Joint Committee on Cancer (AJCC) classifications for staging of epithelial cancers of the esophagus and esophagogastric junction[16]. As this classification was updated in 2017 to differentiate T1a from T1b lesions, cases conducted prior to 2017 were staged in this study per the updated criteria based on findings present in EUS and pathology reports[17]. The level of tumor invasion was consistently described in both types of reports, allowing for pre-2017 to be classified using the 8th edition TNM staging. Descriptions of submucosal invasion as "irregularities between the mucosal and submucosal border" were used to determine T1b or beyond staging in written reports. The presence of notable para-esophageal lymph nodes on EUS was also denoted in reports including comments regarding diagnostic value. Pathologic diagnosis was determined by pathologists' interpretation of tissue sample taken during endoscopy either by EMR, ESD, esophagectomy or forceps biopsy. For the purposes of this study, deep invasion (DI) was defined as a T2 lesion or more (Figure 2).

Outcomes

Patient characteristics and clinical data were extracted from chart review including birth date, sex, ethnicity, type of esophageal cancer (adenocarcinoma, squamous cell carcinoma or other cancer), diagnosis of Barrett's esophagus. EGD/EUS written procedure reports were used to extract data for the following characteristics: Presence of esophageal ulceration, size of tumor, presence of notable para-esophageal lymph nodes, and T staging per EUS. If unavailable in the EUS report, the presence of ulceration and size of tumor was reported *via* an initial EGD report if done less than 3 mo prior to EUS procedure date. Either biopsy or resection method after EUS was recorded as well. Data from pathology after EMR, ESD, esophagectomy, or forceps biopsy included size and grade of tumor, lateral and deep margins status, the presence of lympho-vascular invasion, and TNM-staging identified on the specimen.

Statistical analysis

IBM SPSS Statistics 20 was used for all statistical analysis. Frequencies and percentages were calculated for all nominal and ordinal variables. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value and Accuracy of EUS in identifying sub-mucosal invasion in histological verified T1 tumors were calculated. Moreover, DI of tumor on histology (defined as T2 or beyond) and clinical characteristics significantly associated with DI were identified by using chi-square test. P value < 0.05 was considered significant for all comparisons.

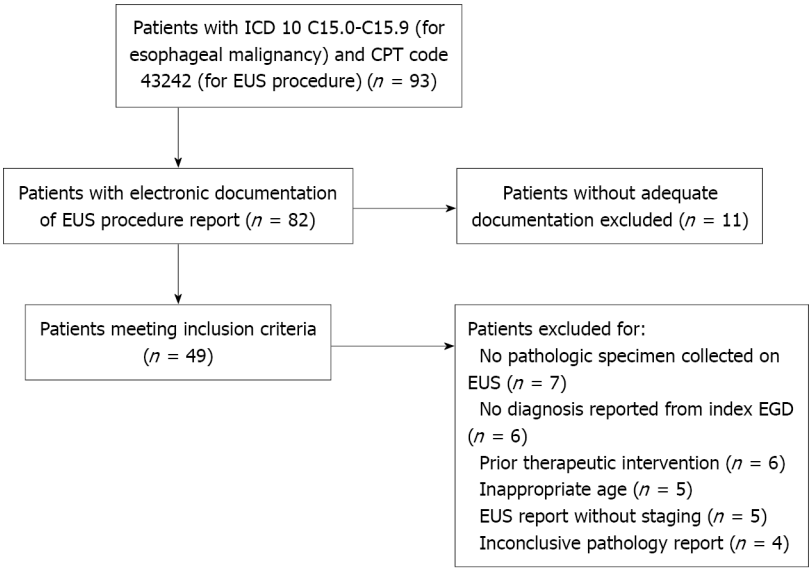

Figure 1 Patient recruitment with relevant exclusion criteria. EUS: Endoscopic ultrasound; EGD: Esophagogastroduodenoscopy.

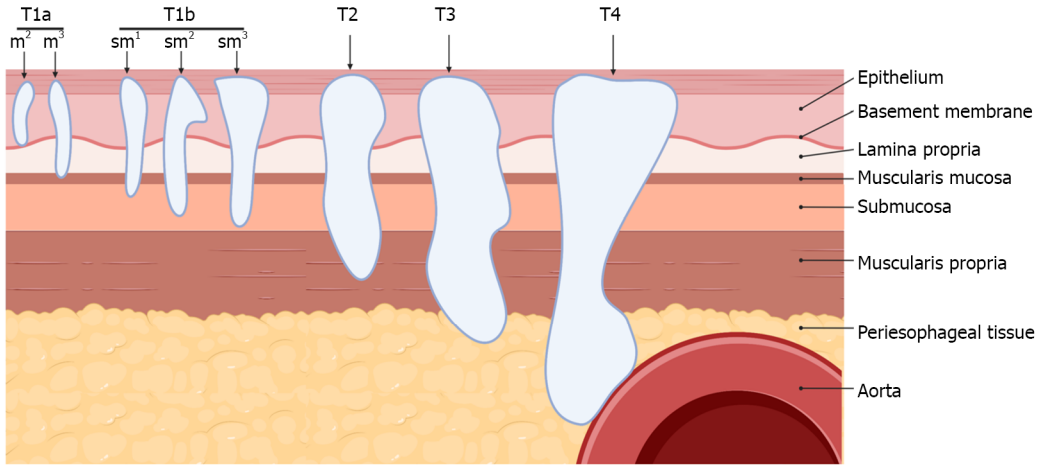

Figure 2 An illustration depicting the sub-classification of esophageal cancer stage. T1b lesion invades the submucosal layer and are stratified into sm^1, sm^2, and sm^3 lesions according to involvement of the first, middle, and deep one-thirds of the submucosa, respectively[16]. Image created in BioRender.

RESULTS

A total of 49 patients were identified for the study. Table 1 summarizes the demographics and clinical characteristics of all patients. Majority of them were males and white, 85.7% and 87.5%, respectively. Adenocarcinoma was the predominant type of cancer (89.8%) among all patients. Prior diagnosis of Barrett's esophagus was present in 65.3% patients. 30.6% of patients were noted to have esophageal ulceration during endoscopy. 39.6% of the patients had tumor size of > 2 cm on visual inspection. EUS identified non-diagnostic lymphadenopathy in 50% of patients, of which none had reported findings for diagnostic lymph node assessment per EUS criteria (*i.e.* size, shape, border, echogencity)[18]. On EUS, 48.9%, 20.4%, 8.2% and 22.4% of patients had T1a, T1b, T2 and T3 tumors, respectively. Subsequently, patients underwent EMR (51%), ESD (10.2%), esophagectomy (30.6%), and diagnostic biopsy (8.2%). On histological examination, 40.8%, 26.5%, 10.2% and 22.4% of patients had T1a, T1b, T2 and T3 tumors. Lympho-vascular invasion was found in 24.4% of all patients.

Table 2 summarizes T stages on EUS against the stage found on final histology. Among all patients with histological T1a (n = 20), 85.0% were correctly labeled as T1a by EUS (17/20), while 15.0% (3/20) were labeled as T1b. Among 13 histologically verified T1b patients, only 46.2% (6/13) were correctly identified as T1b on EUS. Similarly, among 5 T2 patients, only 3 were correctly identified as T2 by EUS. All 11 T3 patients were correctly identified as T3 by EUS. Overall EUS T stage was concordant with histological T stage in 75.5% of patients (37/49).

Table 1 Basic demographics and clinical characteristics of all patients

Variable		Number/Total (*n*/*N*)	Percentage (%)
Gender	Males	42/49	85.7
Ethnicity	Caucasian	42/48	87.5
	Hispanic	1/48	2.1
	Asian	5/48	10.4
Type of cancer	Adenocarcinoma	44/49	89.8
	SCC	5/49	10.2
Degree of differentiation	Invasive well differentiated	18/39	46.2
	Invasive moderately differentiated	19/39	48.7
	Invasive poorly differentiated	4/39	10.3
History of Barrett's esophagus	Yes	32/49	65.3
Esophageal ulceration	Yes	15/49	30.6
Tumor size	< 1 cm	6/48	12.5
	1 – < 1.5 cm	12/48	25
	≥ 1.5 - < 2 cm	11/48	22.9
	≥ 2 cm	19/48	39.6
Lymphadenopathy	Yes (only non-diagnostic EUS features)	24/48	50.0
EUS stage	T1a	24/49	48.9
	T1b	10/49	20.4
	T2	4/49	8.2
	T3	11/49	22.4
	T4	0/49	0
Specimen collection method	Biopsy	4/49	8.2
	EMR	25/49	51.0
	ESD	5/49	10.2
	Esophagectomy	15/49	30.6
Lympho-vascular invasion	Yes	12/49	24.4
Pathological staging	T1a	20/49	40.8
	T1b	13/49	26.5
	T2	5/49	10.2
	T3	11/49	22.4
Tumor recurrence	Yes	5/44	11.4

n: Number of patients with demographic or clinical characteristic present; *N*: Number of patients with clinical data available regarding the presence or absence of each demographic or clinical characteristic. EMR: Endoscopic mucosal resection; ESD: Submucosal dissection; EUS: Endoscopic ultrasound; SCC: Squamous cell carcinoma.

Among these cancer patients, 33 out of 49, had either T1a or T1b cancer on histology. Table 3 shows sensitivity, specificity, PPV, NPV, and diagnostic accuracy of EUS in identifying sub-mucosal invasion (T1b) in T1 Cancers. Although EUS was reasonably specific in ruling out sub-mucosal invasion when it was not present (85.0%), it had a poor sensitivity to identify sub-mucosal invasion when it truly was present (53.9%). EUS had an overall accuracy of 72.7% in identifying sub-mucosal invasion in T1 cancers.

DI of tumor on histology was defined as T2 or beyond and endoscopic characteristics significantly associated with DI are depicted in Table 4. Proportions of patients with DI having the significant endoscopic parameters were compared to patients without DI. Tumor size ≥ 2 cm on visual inspection was significantly associated with DI of cancer on histology. 50% of DI cancers and 21.2% of superficial

Table 2 Frequencies and proportions of endoscopic ultrasound staging across pathological staging categories, *n* (%)

			Pathologic stage			
			T1a, *N* = 20	T1b, *N* = 13	T2, *N* = 5	T3, *N* = 11
EUS stage	T1a	*n*/*N* (%)	17/20 (85.7)	6/13 (46.2)	1/5 (20)	0/11 (0)
	T1b	*n*/*N* (%)	3/20 (14.2)	6/13 (46.2)	1/5 (20)	0/11 (0)
	T2	*n*/*N* (%)	0/20 (0)	1/13 (7.7)	3/5 (60)	0/11 (0)
	T3	*n*/*N* (%)	0/20 (0)	0/13 (0)	0/5 (0)	11/11 (100)

EUS: Endoscopic ultrasound.

Table 3 Sensitivity, specificity and diagnostic accuracy of endoscopic ultrasound staging in identifying submucosal invasion (T1b) in T1 cancers

		Submucosal invasion on path						
		Yes (T1b), *N* = 13	No (T1a), *N* = 20	Sensitivity	Specificity	PPV	NPV	Accuracy
Submucosal invasion on EUS	Yes	7	3	53.9%	85.0%	70%	73.9%	72.7%
	No	6	17					

EUS: Endoscopic ultrasound.

Table 4 Proportions of patients with deep invasion (T2 and beyond) having the significant endoscopic or pathologic parameter compared to proportions of patients without deep invasion

Deep invasion on pathology		Endoscopic parameter		
		Tumor size ≥ 2 cm on visual inspection	Presence of esophageal ulceration	Tumor size ≥ 2 cm on visual inspection & presence of esophageal ulceration
Yes (T2 and beyond)	n_1/N_1 (%)	13/16 (81.2)	8/16 (50.0)	7/16 (43.8)
No (T1a and T1b)	n_2/N_2 (%)	6/32 (18.8)	7/33 (21.2)	2/33 (6.1)
P value[a]		< 0.001	0.0403	0.0014
Deep invasion on pathology		Degree of differentiation on pathology		
		Well-Differentiated	Moderately to poorly differentiated	
Yes (T2 and beyond)	n_1/N_1 (%)	2/12 (16.7)	10/12 (83.3)	
No (T1a and T1b)	n_2/N_2 (%)	14/27 (53.6)	13/27 (46.4)	
P value[a]		0.0392	0.0392	

[a]*P* value derived from chi-square test to compare proportions in each column for patients with deep invasion ("Yes" row) for each endoscopic or pathologic parameter and without deep invasion ("No" row).
n_1: Number of patients with factor being assessed and deep invasion on pathology; N_1: Number of patients with deep invasion on pathology and clinical data available regarding the presence or absence of each factor; n_2: Number of patients with factor being assessed and no deep invasion on pathology; N_2: Number of patients without deep invasion on pathology and clinical data available regarding the presence or absence of each factor.

cancers had ulceration on EGD. Similarily, pathologic factors associated with DI are also noted. As the tumors' degree of differentiation went from well- to poor-, likelihood of DI also significantly increased (*P* = 0.0392).

The EUS parameter associated with DI was the presence of notable (non-diagnostic) para-esophageal lymph node, as depicted in Table 5. Importantly, the presence of notable para-esophageal lymph nodes, whether characterized as lymphadenopathy or described as "prominent", was typically without significant diagnostic findings including size, shape, border, or echogencity. Thus, none of the reported notable lymph nodes met EUS criteria predictive for lymph node metastasis[18].

Table 5 Proportions of patients with deep invasion (T2 and beyond) having the endoscopic ultrasound parameters assessed compared to proportions of patients without deep invasion

Deep invasion on pathology		EUS parameter	
		Presence of notable (but non-diagnostic) para-esophageal lymph nodes on EUS	Presence of positive lymph nodes by EUS criteria
Yes (T2 and beyond)	n_1/N_1 (%)	13/16 (81.2)	0/16 (0)
No (T1a and T1b)	n_2/N_2 (%)	11/33 (33.3)	0/33 (0)
P value[a]		< 0.001	N/A

[a]*P* value derived from chi-square test done to compare proportion of patients with deep invasion for each endoscopic or pathologic parameter ("Yes" row) to proportion of patients without deep invasion ("No" row).

n_1: Number of patients with factor being assessed AND deep invasion on pathology; n_2: Number of patients with factor being assessed AND no deep invasion on pathology; N_1: Number of patients with deep invasion on pathology and clinical data available regarding the presence or absence of each factor; N_2: Number of patients without deep invasion on pathology and clinical data available regarding the presence or absence of each factor. EUS: Endoscopic ultrasound; N/A: Not applicable.

Several studies indicate that endoscopic findings of tumor size ≥ 2 cm and the presence of ulceration are associated with deep invasive tumors that are staged T2 and beyond[13-15]. Thus, the lack of these findings on endoscopy would suggest more superficial cancers. Cases without these findings on endoscopy were assessed to identify if the addition of EUS identified DI, when a superficial cancer is suspected. This is critically important as DI warrants esophagectomy over EMR/ESD.

DISCUSSION

The utility of pre-intervention EUS of the esophageal cancer is influenced by its accuracy in T staging. Early studies have reported the accuracy at 84%[19]. Additional studies reported the EUS accuracy ranging from 75%-82% for T1 esophageal cancer as compared to 88-100% for T4 lesions[20]. In current study including the sub-classification of T1a and T1b, EUS T staging was found to be concordant with histology 75.5% of the time.

In a study focusing on early-stage esophageal cancer subset, the lower accuracy of EUS reflects on the imprecision of distinguishing T1a and T1b lesions, which in turn reflects on its limitation of subclassifying a lesion into superficial (sm1) *vs* deep submucosal invasion (sm^2 and sm^3) cancer. In a systematic review and subsequent meta-analysis, Thosani *et al*[21] reported sensitivities and specificities for EUS in determining T1a and T1b staging. For T1b, the sensitivity and specificity were both 0.86. In staging T1b lesions, our study indicated EUS was reasonably specific (0.83) in ruling out sub-mucosal invasion; however, it had relatively poor sensitivity (0.54) in identifying the invasion. Overall accuracy of EUS in staging T1b lesions in our study was 72.7%. Similar issues were highlighted by another retrospective cohort study involving 131 cases of patient undergoing EUS for early esophageal cancer staging. In the study, EUS found no submucosal involvement in 80% of cases, however, histopathological evaluation after EMR determined either submucosal invasion, positive resection margin for cancer, or lymphovascular invasion in 24% of these cases[11].

The value of pre-intervention EUS evaluation in suspected early-stage cancer relies on whether it provides change-of-management information for endoscopic intervention such as EMR or ESD. Clear evidence suggestive of deep muscular involvement (*i.e.* DI) or presence of significant adenopathy would preclude such endoscopic intervention.

Established endoscopic predictive signs of DI (*i.e.* T2 and beyond) include size ≥ 2 cm, moderate to poorly differentiated cancer, and the presence of ulceration[13-15]. In our study, 81.2% of lesions with deep invasion were ≥ 2 cm, validating this parameter association with deep invasion. The presence of esophageal ulceration had a similar trend with 50.0% of lesions with deep invasion having ulceration, significantly more than the 21.2% of superficial cancers with ulceration. Both endoscopic parameters of a tumor size ≥ 2 cm and the presence of esophageal ulceration were present in 43.8% of cases with DI and only 6.1% of cases without DI. The association between the investigated endoscopic features with deep invasive esophageal lesions is further cemented through these results. It was also found that the presence of moderate to poor differentiation was associated with deep invasion in 83.3% of cases. The presence of these parameters indicates a higher likelihood for deep invasion and EUS is warranted as prior studies and our study indicate its accuracy in staging lesions that are T2 and beyond. Particularly, size, ulceration, and degree of differentiation can be determined on initial diagnostic EGD with biopsy, highlighting their presence as determining indicators to pursue an EUS staging procedure. Differentiating between superficial and deep cancer helps to determine intervention and has significant implications downstream in survival, complications, and cost-saving measures[22].

Table 6 Cases of endoscopic ultrasound concordance and discordance with endoscopic parameters suggesting superficial cancer

Endoscopic Parameter(s) Associated with superficial cancer	Cases of EUS revealing superficial cancer (leading to EMR or ESD)	Cases of EUS revealing DI (Esophagectomy performed)	Frequency EUS changes management (%)
Tumor size < 2 cm	27	2	6.9
Lack of ulceration	26	8	23.5
Tumor size < 2 cm & lack of ulceration	20	1	4.8

EUS: Endoscopic ultrasound; ESD: Submucosal dissection; EMR: Endoscopic mucosal resection; DI: Deep invasion.

If endoscopic parameters of a tumor size ≥ 2 cm and ulceration are not present, it could be inferred that the relevant lesion is more likely superficial. Thus, we reviewed the cases with lesions < 2 cm or ulceration among our group to see if EUS noted DI. Of 29 patients with tumors < 2 cm in size, EUS identified DI and suggested esophagectomy in 2. Of 34 patients without ulceration, EUS identified DI cancer and suggested esophagectomy in 8 of them. Seven of these patient's had other signs of deep invasion including tumor size ≥ 2 cm or moderately to poorly differentiated cancer. Of 21 patients without esophageal ulceration and with a tumor size < 2 cm, EUS identified 1 case of DI and changed management to esophagectomy, as noted in Table 6. Given the small sample size of these subgroups, significance is difficult to determine, however, we observed that EUS only infrequently changed the outcome in the patients based on prior endoscopic features.

The finding of any notable (non-diagnostic) para-esophageal lymph nodes on EUS was significantly associated with DI cancers per data presented in Table 5 above. In both deep and superficial cancers, all notable para-esophageal lymph nodes described in procedure reports were not malignant by EUS criteria (size great than 10 mm, round appearance, well-demarcated, and homogeneous hypoechogenic appearance) and did not significantly alter clinical management[18,23]. Among these patients, no lymph nodes were noted on the staging computed tomography imaging. In the 11 superficial cancers with non-diagnostic para-esophageal lymph nodes, the finding did not alter management after undergoing endoscopic intervention based on EUS findings. On follow up, all 11 patients had no additional treatment for esophageal cancer and no evidence of recurrence from the date of the studied EUS procedure (ranging from 01/2005 to 03/22022) until present day. In all 13 patients who had non-diagnostic para-esophageal lymph nodes in addition to deep invasion on pathology, endoscopic parameters associated with deep invasion (tumor size ≥ 2 cm, presence of ulceration, and moderate to poorly differentiated cancer) were present as well. All 13 patients were considered for esophagectomy, with a majority undergoing surgical resection. While non-diagnostic para-esophageal lymph nodes are more often present in deeper cancers, their presence does not appear to change management decisions.

The present study presents a limitation of a single-center retrospective study with a study population that lacks external validity. The volume of patients included in this study may not adequately depict the population of patients undergoing EUS procedures. Patients were predominantly white males, and as discussed, esophageal cancer occurs globally at higher rates in certain subpopulations throughout the world. Additionally, cases were analyzed using written reports of EUS procedures without any validation of the imaging findings directly. Written reports of submucosal invasion are limited by endoscopist interpretation without reviewing all imaging findings, which was not possible in all cases. Cases where EUS did not determine staging were excluded, thus limiting analysis of instances where EUS was not able to assess depth of invasion at all; however, the vast majority of cases where EUS did not yield staging did not visualize cancerous lesions on endoscopy. A majority of patients had T1a lesions, adding selection bias to our study limited by the types of patients referred to our single academic medical. Our study selects for patients living in the US with adequate access to care to undergo the aforementioned procedures.

To further substantiate our findings, a prospective multi-center analyses would be ideal to verify operability and accuracy. To improve on the limitation of endoscopic ultrasonography precision in detecting the subtle submucosal invasion further investigation may require applications of technologies such as photoacoustic or scanning laser acoustic microscopy or optical coherence tomography, which could provide higher axial resolution than ultrasonography at meaningful penetration depths of a few millimeters[24,25].

CONCLUSION

In conclusion, EUS has limited effectiveness in distinguishing sublayer involvement of superficial esophageal lesions. Since pre-intervention EUS in evaluation of endoscopically and imaging suggested superficial cancer may be limited, we suggest that the role of EUS in this setting may be assessed with careful endoscopic examination and approached in the following way: When initial endoscopic

indicators suggest deep invasion, EUS has utility in investigating the DI cancer. In cases where deep cancer is not suspected based on the endoscopic parameters, one may consider directly proceeding with endoscopic intervention as it is cost effective and provides more accurate T staging by histology.

ARTICLE HIGHLIGHTS

Research background

Endoscopic ultrasound (EUS) has been utilized as the most accurate imaging modality for primary tumor staging in esophageal cancer. Primary tumor staging is key in management as cancers with submucosal invasion warrant esophagectomy while more superficial cancers are managed with endoscopic interventions like endoscopic muscoal resection (EMR) and endoscopic submucosal dissection (ESD). Studies exist that correlate endoscopic parameters with biopsy assessments to identify esophageal cancers with deep invasion in lieu of EUS.

Research motivation

EUS has proven to be useful in identifying advances stage tumors. Its usefulness in early-stage cancers has been more controversial. We wanted to assess how EUS influences management in early-stage esophageal cancers as the presence of submucosal invasion warrants surgery instead of endoscopic intervention.

Research objectives

The objectives of this study included evaluating the diagnostic capabilities of EUS in primary staging of esophageal cancers. We also sought to identify if EUS could reliably discriminate between early-stage cancers with and without submucosal invasion. The study aimed to substantiate endoscopic parameters associated with deep esophageal cancer *vs* superficial esophageal cancer. Finally, our objective was to determine how often EUS changed management by identifying submucosal invasion in cancers with endoscopic parameters associated with superficial esophageal cancers.

Research methods

A retrospective cohort study was utilized to assess patients who had undergone primary staging of esophageal cancer *via* EUS at a tertiary medical center. Case data was gathered *via* chart review and statistical analysis was conducted to assess the accuracy of EUS, endoscopic parameters associated with deep invasion, and the frequency EUS findings changed management when endoscopic parameters suggested a superficial cancer.

Research results

In staging T1b lesions, EUS was specific in ruling in submucosal invasion but had relatively poor sensitivity in ruling out T1b lesions. Endoscopic parameters of tumor size > 2 cm and ulceration were associated with deep invasion (T2 and beyond). The EUS parameter of notable para-esophageal lymph was associated with deep invasion, while on pathology, moderate to poorly differentiated cancers were associated with deep invasion. When known endoscopic signs of deep invasion were not present, EUS altered management from EMR/ESD to esophagectomy in < 5% of cases.

Research conclusions

EUS is accurate in staging deep invasive cancers (T2 or beyond) and reliably excludes deep invasive cancers from T1 Lesions. EUS is limited in distinguishing between T1a and T1b lesions. We reinforced that tumor size > 2 cm, lymph node involvement and poor differentiation are endoscopic parameters associated with deep invasion (T2 or beyond). EUS infrequently changes the outcome in the patients based on prior endoscopic features. While EUS may improve accuracy, our data indicates that it rarely finds deep submucosal invasion to warrant esophagectomy over EMR/ESD when endoscopic features suggest a superficial cancer (T1a or more superficial).

Research perspectives

Future directions should focus on expanding the external validity of this study through either a larger sample size or prospective cohort analysis. This study also warrants further investigation on modalities for detecting the subtlety of submucosal invasion, including applications of technologies such as photoacoustic or scanning laser acoustic microscopy or optical coherence tomography.

FOOTNOTES

Author contributions: Kahlon S, Aamar A, and Urayama S designed the research study; Kahlon S and Aamar A

performed the research; Kahlon S and Butt Z conducted the statistical analysis; Kahlon S and Urayama S analyzed the data and wrote the manuscript; All authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed and approved by the UC Davis Institutional Review Board [(Approval No. 1816393-1]).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous data that were obtained from electronic medical record. A HIPPA waiver was provided by institutional IRB.

Conflict-of-interest statement: Shiro Urayama, MD has financial relationships with the following entities: Olympus America Inc., Noah Medical. Neither entity is directly involved in this work and no financial and/or material support was received for this research or the creation of this work. All other authors have no relationships relevant to the contents of this paper to disclose.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at sakahlon@ucdavis.edu. Participants consent was not obtained but the presented data are anonymized and risk of identification is low.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Fan JR

REFERENCES

1 **Napier KJ**, Scheerer M, Misra S. Esophageal cancer: A Review of epidemiology, pathogenesis, staging workup and treatment modalities. *World J Gastrointest Oncol* 2014; **6**: 112-120 [PMID: 24834141 DOI: 10.4251/wjgo.v6.i5.112]
2 **Siegel RL**, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin* 2022; **72**: 7-33 [PMID: 35020204 DOI: 10.3322/caac.21708]
3 **Pohl H**, Sirovich B, Welch HG. Esophageal adenocarcinoma incidence: are we reaching the peak? *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 1468-1470 [PMID: 20501776 DOI: 10.1158/1055-9965.EPI-10-0012]
4 **Ajani JA**, D'Amico TA, Bentrem DJ, Chao J, Corvera C, Das P, Denlinger CS, Enzinger PC, Fanta P, Farjah F, Gerdes H, Gibson M, Glasgow RE, Hayman JA, Hochwald S, Hofstetter WL, Ilson DH, Jaroszewski D, Johung KL, Keswani RN, Kleinberg LR, Leong S, Ly QP, Matkowskyj KA, McNamara M, Mulcahy MF, Paluri RK, Park H, Perry KA, Pimiento J, Poultsides GA, Roses R, Strong VE, Wiesner G, Willett CG, Wright CD, McMillian NR, Pluchino LA. Esophageal and Esophagogastric Junction Cancers, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2019; **17**: 855-883 [PMID: 31319389 DOI: 10.6004/jnccn.2019.0033]
5 **Othman MO**, Lee JH, Wang K. Clinical Practice Update on the Utility of Endoscopic Submucosal Dissection in T1b Esophageal Cancer: Expert Review. *Clin Gastroenterol Hepatol* 2019; **17**: 2161-2166 [PMID: 31401148 DOI: 10.1016/j.cgh.2019.05.045]
6 **Heidemann J**, Schilling MK, Schmassmann A, Maurer CA, Büchler MW. Accuracy of endoscopic ultrasonography in preoperative staging of esophageal carcinoma. *Dig Surg* 2000; **17**: 219-224 [PMID: 10867453 DOI: 10.1159/000018838]
7 **Hu Y**, Fu JH, Rong TH, Xu GL, Li XD, Zhang PY, Yang H, Zhu ZH, Zhang SY. [Application of endoscopic ultrasonography to preoperative clinical staging of esophageal cancer]. *Ai Zheng* 2005; **24**: 1358-1362 [PMID: 16552963]
8 **Mennigen R**, Tuebergen D, Koehler G, Sauerland C, Senninger N, Bruewer M. Endoscopic ultrasound with conventional probe and miniprobe in preoperative staging of esophageal cancer. *J Gastrointest Surg* 2008; **12**: 256-262 [PMID: 17823841 DOI: 10.1007/s11605-007-0300-2]
9 **Shimpi RA**, George J, Jowell P, Gress FG. Staging of esophageal cancer by EUS: staging accuracy revisited. *Gastrointest Endosc* 2007; **66**: 475-482 [PMID: 17725937 DOI: 10.1016/j.gie.2007.03.1051]
10 **DaVee T**, Ajani JA, Lee JH. Is endoscopic ultrasound examination necessary in the management of esophageal cancer?

World J Gastroenterol 2017; **23**: 751-762 [PMID: 28223720 DOI: 10.3748/wjg.v23.i5.751]

11 **Pouw RE**, Heldoorn N, Alvarez Herrero L, ten Kate FJ, Visser M, Busch OR, van Berge Henegouwen MI, Krishnadath KK, Weusten BL, Fockens P, Bergman JJ. Do we still need EUS in the workup of patients with early esophageal neoplasia? A retrospective analysis of 131 cases. *Gastrointest Endosc* 2011; **73**: 662-668 [PMID: 21272876 DOI: 10.1016/j.gie.2010.10.046]

12 **Young PE**, Gentry AB, Acosta RD, Greenwald BD, Riddle M. Endoscopic ultrasound does not accurately stage early adenocarcinoma or high-grade dysplasia of the esophagus. *Clin Gastroenterol Hepatol* 2010; **8**: 1037-1041 [PMID: 20831900 DOI: 10.1016/j.cgh.2010.08.020]

13 **Gamboa AM**, Kim S, Force SD, Staley CA, Woods KE, Kooby DA, Maithel SK, Luke JA, Shaffer KM, Dacha S, Saba NF, Keilin SA, Cai Q, El-Rayes BF, Chen Z, Willingham FF. Treatment allocation in patients with early-stage esophageal adenocarcinoma: Prevalence and predictors of lymph node involvement. *Cancer* 2016; **122**: 2150-2157 [PMID: 27142247 DOI: 10.1002/cncr.30040]

14 **Krill T**, Baliss M, Roark R, Sydor M, Samuel R, Zaibaq J, Guturu P, Parupudi S. Accuracy of endoscopic ultrasound in esophageal cancer staging. *J Thorac Dis* 2019; **11**: S1602-S1609 [PMID: 31489227 DOI: 10.21037/jtd.2019.06.50]

15 **Ruan R**, Chen S, Tao Y, Yu J, Zhou D, Cui Z, Shen Q, Wang S. Retrospective analysis of predictive factors for lymph node metastasis in superficial esophageal squamous cell carcinoma. *Sci Rep* 2021; **11**: 16544 [PMID: 34400710 DOI: 10.1038/s41598-021-96088-y]

16 **Rice TW**, Patil DT, Blackstone EH. 8th edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to clinical practice. *Ann Cardiothorac Surg* 2017; **6**: 119-130 [PMID: 28447000 DOI: 10.21037/acs.2017.03.14]

17 **Zhang D**, Zheng Y, Wang Z, Huang Q, Cao X, Wang F, Liu S. Comparison of the 7th and proposed 8th editions of the AJCC/UICC TNM staging system for esophageal squamous cell carcinoma underwent radical surgery. *Eur J Surg Oncol* 2017; **43**: 1949-1955 [PMID: 28716377 DOI: 10.1016/j.ejso.2017.06.005]

18 **Catalano MF**, Sivak MV Jr, Rice T, Gragg LA, Van Dam J. Endosonographic features predictive of lymph node metastasis. *Gastrointest Endosc* 1994; **40**: 442-446 [PMID: 7926534 DOI: 10.1016/s0016-5107(94)70206-3]

19 **Saunders HS**, Wolfman NT, Ott DJ. Esophageal cancer. Radiologic staging. *Radiol Clin North Am* 1997; **35**: 281-294 [PMID: 9087204 DOI: 10.1016/S0033-8389(22)00708-4]

20 **Dhupar R**, Rice RD, Correa AM, Weston BR, Bhutani MS, Maru DM, Betancourt SL, Rice DC, Swisher SG, Hofstetter WL. Endoscopic Ultrasound Estimates for Tumor Depth at the Gastroesophageal Junction Are Inaccurate: Implications for the Liberal Use of Endoscopic Resection. *Ann Thorac Surg* 2015; **100**: 1812-1816 [PMID: 26233274 DOI: 10.1016/j.athoracsur.2015.05.038]

21 **Thosani N**, Singh H, Kapadia A, Ochi N, Lee JH, Ajani J, Swisher SG, Hofstetter WL, Guha S, Bhutani MS. Diagnostic accuracy of EUS in differentiating mucosal versus submucosal invasion of superficial esophageal cancers: a systematic review and meta-analysis. *Gastrointest Endosc* 2012; **75**: 242-253 [PMID: 22115605 DOI: 10.1016/j.gie.2011.09.016]

22 **Thakkar S**, Kaul V. Endoscopic Ultrasound Staging of Esophageal Cancer. *Gastroenterol Hepatol (N Y)* 2020; **16**: 14-20 [PMID: 33867884]

23 **Badreddine RJ**, Prasad GA, Lewis JT, Lutzke LS, Borkenhagen LS, Dunagan KT, Wang KK. Depth of submucosal invasion does not predict lymph node metastasis and survival of patients with esophageal carcinoma. *Clin Gastroenterol Hepatol* 2010; **8**: 248-253 [PMID: 19948247 DOI: 10.1016/j.cgh.2009.11.016]

24 **Zhang K**, Qiu J, Yang F, Wang J, Zhao X, Wei Z, Ge N, Chen Y, Sun S. Photoacoustic endoscopy and EUS: Shaking the future of multimodal endoscopy. *Endosc Ultrasound* 2022; **11**: 1-3 [PMID: 35229746 DOI: 10.4103/EUS-D-22-00011]

25 **Tsai TH**, Fujimoto JG, Mashimo H. Endoscopic Optical Coherence Tomography for Clinical Gastroenterology. *Diagnostics (Basel)* 2014; **4**: 57-93 [PMID: 26852678 DOI: 10.3390/diagnostics4020057]

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2023 June 16; 15(6): 458-468

DOI: 10.4253/wjge.v15.i6.458

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Multicenter evaluation of recurrence in endoscopic submucosal dissection and endoscopic mucosal resection in the colon: A Western perspective

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Kobayashi N, Japan; Tsou YK, Taiwan

Received: February 20, 2023
Peer-review started: February 20, 2023
First decision: April 13, 2023
Revised: May 12, 2023
Accepted: May 31, 2023
Article in press: May 31, 2023
Published online: June 16, 2023

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Abstract

BACKGROUND

While colon endoscopic mucosal resection (EMR) is an effective technique, removal of larger polyps often requires piecemeal resection, which can increase recurrence rates. Endoscopic submucosal dissection (ESD) in the colon offers the ability for *en bloc* resection and is well-described in Asia, but there are limited studies comparing ESD *vs* EMR in the West.

AIM

To evaluate different techniques in endoscopic resection of large polyps in the colon and to identify factors for recurrence.

METHODS

The study is a retrospective comparison of ESD, EMR and knife-assisted endoscopic resection performed at Stanford University Medical Center and Veterans Affairs Palo Alto Health Care System between 2016 and 2020. Knife-assisted endoscopic resection was defined as use of electrosurgical knife to facilitate snare resection, such as for circumferential incision. Patients ≥ 18 years of age undergoing colonoscopy with removal of polyp(s) ≥ 20 mm were included. The primary outcome was recurrence on follow-up.

RESULTS

A total of 376 patients and 428 polyps were included. Mean polyp size was greatest in the ESD group (35.8 mm), followed by knife-assisted endoscopic resection (33.3 mm) and EMR (30.5 mm) ($P < 0.001$). ESD achieved highest *en bloc*

resection (90.4%) followed by knife-assisted endoscopic resection (31.1%) and EMR (20.2%) (P < 0.001). A total of 287 polyps had follow-up (67.1%). On follow-up analysis, recurrence rate was lowest in knife-assisted endoscopic resection (0.0%) and ESD (1.3%) and highest in EMR (12.9%) (P = 0.0017). *En bloc* polyp resection had significantly lower rate of recurrence (1.9%) compared to non-*en bloc* (12.0%, P = 0.003). On multivariate analysis, ESD (in comparison to EMR) adjusted for polyp size was found to significantly reduce risk of recurrence [adjusted hazard ratio 0.06 (95%CI: 0.01-0.57, P = 0.014)].

CONCLUSION

In our study, EMR had significantly higher recurrence compared to ESD and knife-assisted endoscopic resection. We found factors including resection by ESD, *en bloc* removal, and use of circumferential incision were associated with significantly decreased recurrence. While further studies are needed, we have demonstrated the efficacy of ESD in a Western population.

Key Words: Endoscopic mucosal resection; Endoscopic submucosal dissection; Recurrence; Colonoscopy; Polypectomy

Core Tip: Endoscopic submucosal dissection is an effective and safe technique. Compared to endoscopic mucosal resection, we find that endoscopic submucosal dissection as well as knife-assisted endoscopic resection to achieve higher en bloc resection, circumferential incision, R0 resection as well as lower recurrence rate. While further studies are needed, we have demonstrated the efficacy of endoscopic submucosal dissection in a Western population.

Citation: Wei MT, Zhou MJ, Li AA, Ofosu A, Hwang JH, Friedland S. Multicenter evaluation of recurrence in endoscopic submucosal dissection and endoscopic mucosal resection in the colon: A Western perspective. *World J Gastrointest Endosc* 2023; 15(6): 458-468
URL: https://www.wjgnet.com/1948-5190/full/v15/i6/458.htm
DOI: https://dx.doi.org/10.4253/wjge.v15.i6.458

INTRODUCTION

Large non-pedunculated colorectal polyps are currently removed primarily through endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD)[1]. ESD has been slowly adopted in the United States, limited in large part due to lack of experts, long training required and significantly increased time for resection compared to EMR[2]. As a result, there is limited data for Western experience in ESD. In the largest prospective multicenter study to date in North America, Draganov *et al* [3] identified 399 cases of ESD in the colorectum, identifying an *en bloc* resection rate of 87.2%, and recurrence rate of 2.7% (8 of 296)[3]. With the growing experience in North America in performing ESD, there is increased attention to performance outcomes of ESD compared to EMR. In this study, we seek to evaluate our experience of ESD compared to EMR at two tertiary centers in California.

MATERIALS AND METHODS

Study cohort

We performed a retrospective study evaluating endoscopic resection performed of polyps ≥ 20 mm at two centers (Stanford University Medical Center and Veterans Affairs Palo Alto Health Care System) by two practitioners (JHH and SF), between January 1, 2016, and December 31, 2020. Inclusion criteria included adults age ≥ 18 who presented for colonoscopy with endoscopic removal of polyp ≥ 20 mm in size. Exclusion criteria included age < 18 and pregnancy.

Definitions for endoscopic resection

Endoscopic resection was categorized as EMR, knife-assisted endoscopic resection and ESD. EMR was defined by hot or cold snare resection of the polyp with or without submucosal injection. Knife-assisted endoscopic resection was defined as use of electrosurgical knife to facilitate snare resection, such as for circumferential incision and minimal submucosal dissection with an ESD knife. ESD was defined as use

of electrosurgical knife for circumferential incision and submucosal dissection with the intention of performing a complete *en bloc* resection using the knife (Figure 1)[4]. *En bloc* resection was defined as removal of the polyp in its entirety in one singular piece. Determination of each technique is up to the discretion of the endoscopist. Knife-assisted endoscopic resection was performed when the endoscopist determined at the initial submucosal injection step that full ESD would be too dangerous, typically due to fibrosis or poor scope stability, but that there was a clinical benefit to utilizing an ESD knife to perform selected parts of the procedure.

Endoscopy was performed using high-definition video endoscopes (*e.g.* PCF-H190DL; GIF-1TH190). A transparent cap was attached to the tip of the endoscope for each procedure. Each polyp was carefully examined under both white light and narrow band imaging (NBI)[5] and evaluated to predict histopathological diagnosis and invasion depth. Polyps were characterized by Paris classification[6] as well as by Japan NBI Expert Team (JNET)[7,8]. Submucosal injection was performed using hydroxyethyl starch with dye, saline with dye, ORISE™ gel (Boston Scientific), Eleview™ liquid composition (Aries Pharmaceuticals), or EverLift™ (GI Supply). Lesion marking, mucosal incision, and submucosal dissection were performed using an DualKnife (Olympus), FlushKnife (Fujinon), Hybrid Knife (ERBE) or ProKnife (Boston Scientific) with an electrosurgical generator (ERBE Elektromedizin, Tübingen, Germany). In select cases, the resection site was closed with hemostatic clips, X-Tac (Apollo Endosurgery), or OverStitch (Apollo Endosurgery). Resected specimens were pinned on cork or foam board for better pathologic analysis. The specimens were fixed with formalin[1].

The size of the polyp was determined by using the snare as reference, or if the polyp was removed *en bloc*, was measured against a ruler when it was retrieved from the colon.

Data collection

All procedures performed by SF (Stanford and Veterans Affairs Palo Alto Health Care System) and JHH (Stanford) between January 1, 2016 and December 31, 2020 were reviewed. Data collected included patient demographics (age, sex, race/ethnicity), sedation, bowel preparation, polyp size, location, Paris and JNET classification, history of prior resection, method of resection, *en bloc* removal of polyp, and pathology of the polyp. Bowel preparation was characterized as adequate or inadequate. 30-d complications recorded included bleeding with or without intervention, perforation, small bowel obstruction, abdominal pain, as well as complications unrelated to procedure. Follow-up endoscopic evaluation was measured for presence or absence of recurrence. Follow-up was reviewed up to December 31, 2022. Recurrence was defined as evidence of polyp in the area of the prior resection. During follow-up endoscopy, careful examination was performed in the area of the resection, with both white light and NBI, to evaluate for recurrence. When there was suspicion for recurrence, resection or biopsies were performed of the area. The primary outcome was recurrence on follow-up. Secondary outcomes included *en bloc* resection and complication rates

Specimen histology

Specimen from knife-assisted endoscopic resection and ESD were spread and pinned onto cork or Styrofoam boards immediately following endoscopic resection. The specimens were fixed in 10% buffered formalin, paraffin embedded, and cut into 2-mm-thick slices, prior to evaluation by a pathologist.

Statistical analysis

All analyses were performed with P-value < 0.05 considered significant. All tests were 2-tailed. χ^2 test was performed to compare the frequencies of categorical outcomes and student's t-test was performed to evaluate averages of normally distributed continuous variables. Cox regression analysis was performed to estimate unadjusted and adjusted hazard ratios (HR and aHR) relating potential confounders such as resection technique, age, sex, race, polyp location, prior resection attempt, polyp size, with polyp recurrence.

Ethics statement

This study was performed under the approval of the Institutional Review Board at Stanford University, Stanford, California, United States.

RESULTS

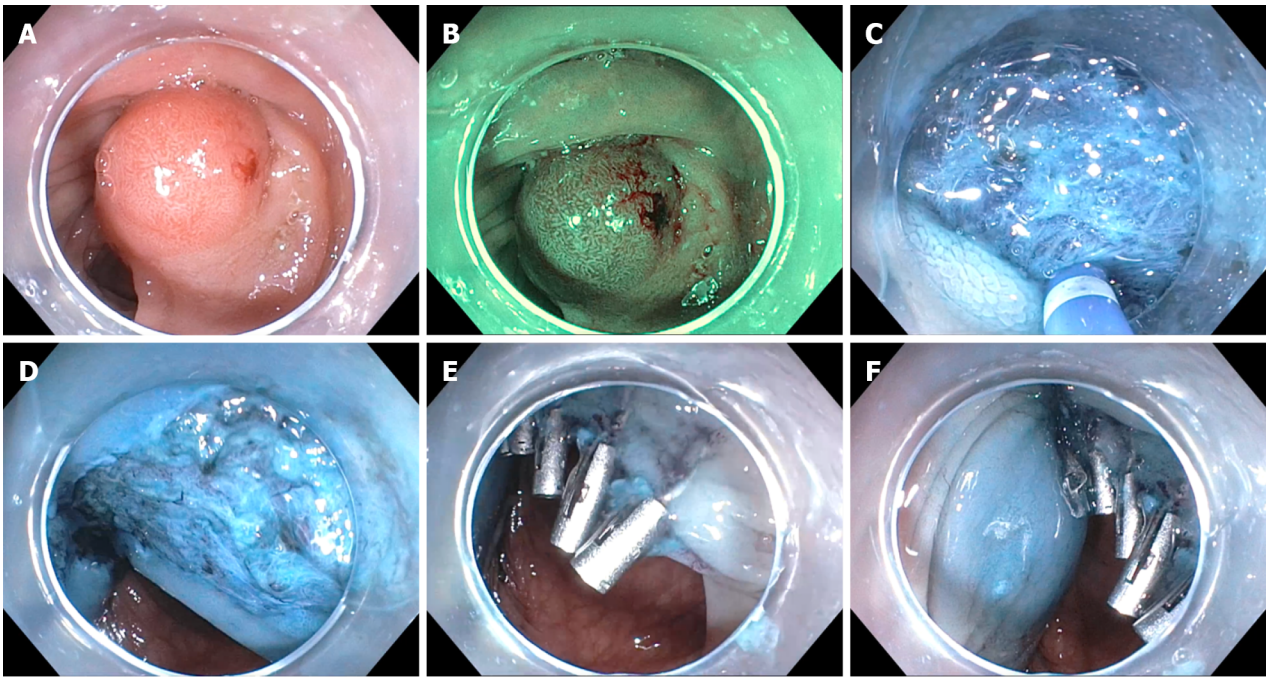
Patient demographics

There were 376 patients included in the study, 122 of whom received ESD, 44 received knife-assisted endoscopic resection and 216 received EMR. A total of 38 patients had more than one ≥ 20 mm polyp removed. There were 6 patients who underwent two resection techniques (*e.g.* EMR and ESD). There was similar distribution in age, sex, race/ethnicity across the three categories of procedures (Table 1). Patients undergoing ESD had a higher likelihood of receiving the procedure under general anesthesia or

Table 1 Patient characteristics by intervention, *n* (%)

N = 376	ESD (*n* = 122)	Knife-assisted endoscopic resection (*n* = 44)	EMR (*n* = 216)	*P* value
Mean age (mean ± SD)	66.9 (11.8)	64.5 (11.8)	66 (9.7)	0.452
Male (%)	78 (63.9)	23 (52.3)	130 (60.2)	0.395
Race/Ethnicity				0.113
White	78 (63.9)	28 (63.6)	144 (66.7)	
Asian	19 (15.6)	6 (13.6)	12 (5.6)	
African American	4 (3.3)	1 (2.3)	11 (5.1)	
Latino	14 (11.5)	6 (13.6)	25 (11.6)	
Other	7 (5.7)	3 (6.8)	24 (11.1)	
Sedation				< 0.001
General anesthesia	11 (9.0)	2 (4.5)	7 (3.2)	
Monitored anesthesia care	93 (76.2)	29 (65.9)	117 (54.2)	
Moderate sedation	17 (13.9)	13 (29.5)	82 (38.0)	
None	1 (0.8)	0 (0.0)	10 (4.6)	
Adequate bowel preparation	121 (99.2)	41 (93.2)	210 (97.2)	0.100

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.



DOI: 10.4253/wjge.v15.i6.458

Figure 1 Endoscopic submucosal dissection. A and B: Steps of endoscopic submucosal dissection includes careful surveillance of the polyp, with techniques including near focus and narrow band imaging; C: Mucosal incision is performed following by submucosal dissection, which is aided by a submucosal lifting agent (in this case a mixture of epinephrine, hetastarch, and indigo carmine); D-F: Following complete resection of the polyp, the complete resection bed is closed, with techniques including clips.

monitored anesthesia care (85.2%) compared to knife-assisted endoscopic resection (70.5%) and EMR (57.4%).

Polyp resection, overall

A total of 428 polyps underwent endoscopic resection, with 258 by EMR and 125 by ESD (Supplementary Table 1). Polyps removed by ESD (35.8 mm) were larger compared to by knife-assisted

endoscopic resection (33.3 mm), which was larger than by EMR (30.5 mm) ($P < 0.001$). ESD achieved the highest *en bloc* resection (90.4%) followed by knife-assisted endoscopic resection (31.1%) and EMR (20.2%) ($P < 0.001$). There was no significant difference in proportion of polyps that had history of prior resection attempt in the three resection techniques. Non-neoplastic polyps were removed more frequently in EMR (5.8%) compared to ESD (0.0%), while cancer was removed more frequently with ESD (13.6%) compared to EMR (3.5%).

Polyp resection, follow-up

EMR (69.0%) and knife-assisted endoscopic resection (71.1%) had greater proportion of patients that underwent follow-up compared to in the ESD group (61.6%), though this was not statistically significant ($P = 0.266$). On evaluation of polyps that received follow-up evaluation (Table 2), ESD had highest rate of *en bloc* resection (89.7%) followed by knife-assisted endoscopic resection (25.0%), followed by EMR (15.2%) ($P < 0.001$). A higher proportion (44.2%) of polyps undergoing ESD were identified in the rectum compared to knife-assisted endoscopic resection and EMR, while a higher percentage of polyps were removed in the right colon by knife-assisted endoscopic resection or EMR. A higher proportion (74.0%) removed by ESD were identified as Paris classification Is, compared to 56.3% for knife-assisted endoscopic resection and 36.0% for EMR. EMR had the longest mean follow-up (516.2 d) compared to ESD (456.8) and knife-assisted endoscopic resection (365.0), though this was not statistically significant ($P = 0.061$). ESD (74.0%) and knife-assisted endoscopic resection (18.8%) had higher R0 resection compared to EMR (4.5%) ($P < 0.001$). There was no recurrence in the knife-assisted endoscopic removal group (0/30). Recurrence rate was lowest in knife-assisted endoscopic resection (0.0%), followed by ESD (1.3%), and highest in EMR (12.9%) ($P = 0.002$).

In categorizing polyps by presence of recurrence (Table 3), there was overall a low proportion of polyps with recurrence (8.4%). Polyps with recurrence had greater mean average size (37.4 *vs* 32.7 mm, $P = 0.202$), though this was not statistically significant. Polyps with recurrence more often had non en bloc resection (91.7% *vs* 61.2%, $P = 0.003$). Polyps with recurrence more often did not undergo circumferential incision (95.8% *vs* 62.7%, $P = 0.001$). Of note, polyps removed with circumferential incision had higher proportion of *en bloc* removal (76.8% *vs* 14.9%, $P < 0.0001$). Recurrence polyps had a higher proportion of polyps that had prior attempt at removal (17.6% *vs* 5.3%), though this was not statistically significant ($P = 0.154$). There was no significant difference in pathology or mean follow-up between the two groups. Compared to no recurrence, polyps with recurrence had higher proportion of R1 (91.7% *vs* 67.7%) and lower proportion of R0 (4.2% *vs* 26.6%) ($P = 0.041$).

Procedural complications

Overall, there was a low patient complication rate [25 patients (6.6%)], with similar proportion of complication (6.5%-6.8%) among the three procedures (Table 4). There were 3 cases of perforation (two ESD and one knife-assisted endoscopic resection). One patient received knife-assisted endoscopic resection of a > 50 mm polyp in cecum involving the ileocecal valve. There was only partial lifting of the lesion with submucosal injection. Dense fibrosis was encountered, and as such the remainder of the resection was performed by piecemeal EMR. Following the procedure, the patient had abdominal pain, and was found to have pneumoperitoneum. The patient underwent exploratory laparotomy with resection of the terminal ileum and proximal colon. Pathology returned as tubular adenoma with focal high-grade dysplasia. In the second case, the patient had a fungating partially obstructing 50 mm mass in ascending colon. Following ESD, five hemostatic clips placed to close the wound. The patient had worsening abdominal pain following the procedure, and perforation was seen on computed tomography, leading to hemicolectomy. Pathology was consistent with tubulovillous adenoma. In the third case, a 30 mm fungating non-obstructing mass was found in the cecum, encasing the appendiceal orifice. A 40 mm specimen was resected *en bloc*. A single small perforation (< 2 mm) occurred, which was closed with a single clip followed by full mucosal closure with an Endoloop and clips. The patient recovered uneventfully.

Predictors of recurrence

On univariate Cox regression, age, sex, race and polyp location were not significant risk factors. Relative to EMR, ESD was found to decrease risk of recurrence [hazard ratio (HR): 0.12 (95%CI: 0.02-0.92), $P = 0.041$]. Completion of circumferential incision, *en bloc* resection as well as R0 resection were found to significantly reduce risk of recurrence (Table 5). On multivariable Cox regression adjusted for polyp size and type of resection (ESD *vs* EMR), ESD significantly reduced risk of recurrence [adjusted HR (aHR): 0.06 (95%CI: 0.01-0.57, $P = 0.014$)] (Table 6). In this analysis, we did not include *en bloc* resection, R0 resection, and presence of circumferential incision as these are factors closely tied with performance of ESD. When evaluating EMR compared to knife-assisted endoscopic resection combined with ESD, on multivariate analysis ESD and knife-assisted endoscopic resection also demonstrated significant decrease in risk of recurrence [aHR: 0.05 (95%CI: 0.01-0.45), $P = 0.008$] (Supplementary Tables 2 and 3). Knife-assisted endoscopic resection was unable to evaluated independently of ESD as there were no cases of recurrence.

Table 2 Characteristics of polyp with follow-up, by intervention, *n* (%)

N = 287	ESD (*n* = 77)	Knife-assisted endoscopic resection (*n* = 32)	EMR (*n* = 178)	*P* value
Size of polyp, mm (mean ± SD)	37.2 (19.7)	32.7 (8.7)	31.4 (11.5)	0.010
En bloc	69 (89.7)	8 (25.0)	27 (15.2)	< 0.001
Location of polyp				< 0.001
Cecum	10 (13.0)	7 (21.9)	47 (26.4)	
Ascending	13 (16.9)	12 (37.5)	63 (35.4)	
Transverse	8 (10.4)	6 (18.8)	45 (25.3)	
Descending	2 (2.6)	4 (12.5)	12 (6.7)	
Sigmoid	10 (13.0)	1 (3.1)	5 (2.8)	
Rectum	34 (44.2)	2 (6.3)	6 (3.4)	
Paris classification				< 0.001
Is	57 (74.0)	18 (56.3)	64 (36.0)	
IIa	16 (20.8)	9 (28.1)	102 (57.3)	
IIb	0 (0.0)	1 (3.1)	2 (1.1)	
IIa+c	2 (2.6)	1 (3.1)	2 (1.1)	
IIc	0 (0.0)	1 (3.1)	0 (0.0)	
Isp	2 (2.6)	2 (6.3)	8 (4.5)	
Pathology				< 0.001
Non-neoplastic	0 (0.0)	1 (3.1)	10 (5.6)	
Neoplastic, no high-grade dysplasia	50 (64.9)	25 (78.1)	152 (85.4)	
High-grade dysplasia	17 (22.1)	6 (18.8)	12 (6.7)	
Cancer	10 (13.0)	0 (0.0)	4 (2.2)	
First follow-up, days (mean ± SD)	456.8 (326.1)	365.0 (230.2)	516.2 (377.7)	0.061
Recurrence	1 (1.3)	0 (0.0)	23 (12.9)	0.0017
Complete resection				< 0.001
R0	57 (74.0)	6 (18.8)	8 (4.5)	
R1	18 (23.4)	26 (81.3)	156 (87.6)	
Rx	2 (2.6)	0 (0.0)	14 (7.9)	

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

DISCUSSION

The development of advanced polypectomy techniques has allowed patients to avoid colorectal surgeries. While ESD is frequently performed in Asia, it is not commonly performed elsewhere including in the West. However, there are several compelling arguments for performance of ESD over EMR in large (≥ 20 mm) polyps. In a recent meta-analysis, Lim *et al*[9] found that ESD of polyps ≥ 20 mm was associated to higher *en bloc* resection [relative risk (RR): 1.9, 95%CI: 1.4-2.7; $P < 0.001$] and lower recurrence (RR 0.19, 95%CI: 0.09-0.43; $P < 0.001$) compared to EMR[9]. Given the benefits of ESD, this has culminated in a multicenter randomized controlled trial based in France led by Jacques *et al*[10] which found ESD to be superior to EMR in *en bloc* resection as well as decreased recurrence[10]. Given advantages seen with ESD, we performed the first North American study comparing ESD to EMR.

In our retrospective comparison of ESD, EMR and knife-assisted endoscopic resection, ESD was able to achieve the highest *en bloc* resection, followed by knife-assisted endoscopic resection; EMR had the lowest *en bloc* resection rate. Recurrence rate was lowest in the ESD (1.3%) and knife-assisted endoscopic resection group (0.0%), and highest in the EMR group (12.9%). On multivariate regression, we found that performance of ESD (in comparison to EMR) significantly decreased recurrence. Increased polyp size significantly increased risk of recurrence. We were able to achieve *en bloc* resection rate of 90.4% with ESD. This is comparable to work by Gupta *et al*[1], in which overall *en bloc* resection rate was

Table 3 Comparison of recurrence with no recurrence

	Recurrence, *n* (%)	No recurrence, *n* (%)	*P* value
Size of polyp, mm (mean ± SD)	37.4 (17.1)	32.7 (13.8)	0.202
Procedure			0.002
ESD	1/24 (4.2)	76/263 (28.9)	
Knife-assisted endoscopic removal	0/24 (0.0)	32/263 (12.2)	
EMR	23/24 (95.8)	155/263 (58.9)	
***En bloc* resection**			0.003
En bloc	2/24 (8.3)	102/263 (38.8)	
Non *en bloc*	22/24 (91.7)	161/263 (61.2)	
Circumferential incision			0.001
Yes	1/99 (1.0)	98/99 (99.0)	
No	23/188 (12.2)	165/188 (87.8)	
Prior resection			0.154
Prior attempt	3/24 (12.5) (17.6)	14/263 (5.3)	
No prior attempt	21/24 (87.5)	249/263 (94.7)	
Pathology			0.691
Non-neoplastic	0/24 (0.0)	11/263 (4.2)	
Neoplastic, no high-grade dysplasia	19/24 (79.2)	208/263 (79.1)	
High-grade dysplasia	4/24 (16.7)	31/263 (11.8)	
Cancer	1/24 (4.2)	13/263 (4.9)	
First follow-up, days (mean ± SD)	498.0 (406.9)	482.0 (348.7)	0.854
Complete resection			0.041
R0	1/24 (4.2)	70/263 (26.6)	
R1	22/24 (91.7)	178/263 (67.7)	
Rx	1/24 (4.2)	15/263 (5.7)	

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

Table 4 Patient complications, *n* (%)

N = 376	ESD (*n* = 122)	Knife-assisted endoscopic resection (*n* = 44)	EMR (*n* = 216)
Complication	8 (6.6)	3 (6.8)	14 (6.5)
Bleeding without intervention	3 (2.5)[1]	1 (2.3)[1]	5 (2.3)
Bleeding with intervention	3 (2.5)	1 (2.3)	1 (0.5)
SBO/partial SBO	0 (0.0)	0 (0.0)	2 (0.9)
Bowel perforation	2 (1.6)	1 (2.3)	0 (0.0)
Abdominal pain	1 (0.8)[1]	1 (2.3)[1]	3 (1.4)
Unrelated complication	0 (0.0)	0 (0.0)	3 (1.4)

[1]One patient had both bleeding without intervention and abdominal pain.
SBO: Small bowel obstruction; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

73.1%, and the rate for the second half of their study was 84.6%. Similarly, our study had ESD recurrence rate of 1.3%, slightly lower than the 4.3% (n = 2) by Gupta *et al*[1] Overall, there was low risk of complication across the three procedures. Under appropriate training, we feel the three procedures to

Table 5 Univariate Cox regression evaluating predictors of recurrence, including endoscopic submucosal dissection versus endoscopic mucosal resection

Covariates	Unadjusted hazard ratio (95%CI)	*P* value
Treatment type		0.041
EMR, pure	Reference	
ESD, pure	0.12 (0.02-0.92)	
Age, per year	1.04 (0.99-1.08)	0.109
Sex		0.898
Female	Reference	
Male	1.06 (0.46-2.40)	
Race		0.139
White	Reference	
Non-White	1.85 (0.82-4.19)	
Polyp location		0.376
Non-rectum	Reference	
Rectum	0.52 (0.12-2.22)	
Prior resection attempt	2.65 (0.76-9.29)	0.127
Polyp size, by mm	1.03 (1.01-1.05)	0.001
Presence of circumferential incision	0.12 (0.02-0.92)	0.041
***En bloc* resection**	0.15 (0.03-0.63)	0.010
JNET classification		
Type 1	Reference	
Type 2A	3.07 (0.41-22.92)	0.273
Type 2B or 3	4.57 (0.41-50.74)	0.216
R0 resection	0.13 (0.02-0.93)	0.042

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; JNET: Japan NBI Expert Team.

Table 6 Multivariate Cox regression evaluating predictors of recurrence

Covariates	Adjusted hazard ratio (95%CI)	*P* value
Treatment type		0.014
EMR, pure	Reference	
ESD, pure	0.06 (0.01-0.57)	
Polyp size, by mm	1.05 (1.02-1.07)	< 0.001

EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

be safe techniques.

While operational proficiency is related to study outcome, in this study we try to evaluate the specific factors that lead to success in reducing polyp recurrence. Specifically, we look at factors such as *en bloc* resection and performance of circumferential incision. Circumferential incision was found to be associated with decreased recurrence. In one evaluation of ESD compared to hybrid ESD (circumferential mucosal incision followed by snare resection), hybrid ESD trended towards lower *en bloc* resection rate and complete resection rate compared to ESD, though this did not reach statistical significance. However, importantly, on surveillance of hybrid ESD by the Korean specialist (n = 21) and United States novice practitioner (n = 9), there was no recurrence in either group[4]. While this study was limited by overall low numbers, it provided early suggestion that circumferential incision alone may help improve

the outcomes of polyp resection compared to EMR. A major advantage of knife-assisted endoscopic resection over ESD is the relative technical simplicity; in particular, circumferential incision is a relatively safe technique that in our experience is easily taught to trainees with sufficient experience in routine colonoscopy. Over time, with increased experience and proficiency performing ESD, we expect that many endoscopists will choose ESD over knife-assisted endoscopic resection to maximize *en bloc* and R0 resection, but our data highlights the generally excellent long-term results of the knife-assisted technique.

While there is justifiable concern about the risk of perforation with ESD, and the 3 cases of perforation in this series were all in the ESD/knife-assisted endoscopic resection group rather than EMR, it is notable that the perforations occurred in very challenging cases where EMR was deemed not feasible, and surgery was the only other viable option. For large lesions involving greater than half the circumference of the lumen, the Japan Gastroenterological Endoscopy Society does not recommend piecemeal EMR, but rather ESD and consideration for surgery if ESD is not endoscopically feasible[8].

There were several limitations for our study. First, retrospective data from only two endoscopists were used. However, given the lack of ESD experts in the country, having 125 cases of ESD is relatively robust. In addition, while more EMR cases could have been achieved by including other endoscopists at the two hospitals included, this would potentially introduce more bias with variation in technique and approach to EMR as well as skill with polypectomy. Another concern is the limited follow-up (67.1%). A lot of the patients were referred for endoscopic removal but received follow-up with the referring provider. Despite reaching out to community providers, we only received limited response. Further, the retrospective nature of EMR and ESD studies introduce selection bias in the determination of which polyp to undergo EMR, ESD, or knife-assisted endoscopic resection. A randomized clinical trial would be ideal but is logistically challenging given the overall low frequency of these procedures.

CONCLUSION

In this multicenter study evaluating ESD, knife-assisted endoscopic resection and EMR, ESD and knife-assisted endoscopic resection were able to achieve higher rates of *en bloc* resection and was able to achieve significantly lower risk of recurrence compared to EMR. Given the results of this study, ESD and knife-assisted endoscopic resection should be strongly considered when possible for polyps ≥ 20 mm to improve *en bloc* and curative resection and decrease risk of recurrence.

ARTICLE HIGHLIGHTS

Research background

Adoption of endoscopic submucosal dissection (ESD) has been slow in the United States, largely related to lack of experts, long training required and significant time for procedure compared to endoscopic mucosal resection (EMR).

Research motivation

In this study, we seek to evaluate our experience of ESD compared to EMR in California.

Research objectives

We evaluate ESD, knife-assisted endoscopic resection as well as EMR to identify factors for recurrence.

Research methods

This was a retrospective comparison performed at two tertiary centers within California between 2016 and 2020. Adult patients that received colonoscopy with endoscopic removal of a polyp at least 20 mm in size were included. Primary outcome of interest was recurrence on follow-up.

Research results

ESD achieved highest en bloc resection followed by knife-assisted endoscopic resection and EMR. On follow-up, recurrence rate was lowest in knife-assisted endoscopic resection (0.0%) and ESD (1.3%), while EMR had the highest recurrence rate (12.9%, $P = 0.0017$).

Research conclusions

In our study, we found that EMR had significantly higher recurrence compared to ESD or knife-assisted endoscopic resection.

Research perspectives

We have demonstrated efficacy of ESD in a Western population.

FOOTNOTES

Author contributions: Wei MT contributed to project conception, data collection, manuscript writing, data analysis, manuscript revision; Zhou MJ, Li AA and Ofosu A contributed to data analysis, manuscript revision; Hwang JH and Friedland S contributed to project conception, data collection, manuscript revision.

Institutional review board statement: This study was performed under the approval of the Institutional Review Board at Stanford University, Stanford, California, USA.

Informed consent statement: Because of retrospective study signed informed consent form is not needed.

Conflict-of-interest statement: Mike T. Wei: Consultant for Neptune Medical, AgilTx, Capsovision; Margaret Zhou and Andrew Ofosu: No conflicts; Andrew Li: Consultant for Neptune Medical; Joo Ha Hwang: Consultant for Olympus, Medtronic, Boston Scientific, Lumendi, Fujifilm, Noah Medical, Neptune Medical, and Micro-Tech; Shai Friedland: Consultant for Intuitive Surgical and Capsovision.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: United States

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S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

REFERENCES

1 **Gupta N**, Rodríguez-Ruiz G, Siddiqui UD, Chapman CG, Donboli K, Hart J, Xiao SY, Waxman I. Endoscopic submucosal dissection for colorectal lesions: outcomes from a United States experience. *Surg Endosc* 2022; **36**: 236-243 [PMID: 33523276 DOI: 10.1007/s00464-020-08262-4]
2 **Herreros de Tejada A**. ESD training: A challenging path to excellence. *World J Gastrointest Endosc* 2014; **6**: 112-120 [PMID: 24748918 DOI: 10.4253/wjge.v6.i4.112]
3 **Draganov PV**, Aihara H, Karasik MS, Ngamruengphong S, Aadam AA, Othman MO, Sharma N, Grimm IS, Rostom A, Elmunzer BJ, Jawaid SA, Westerveld D, Perbtani YB, Hoffman BJ, Schlachterman A, Siegel A, Coman RM, Wang AY, Yang D. Endoscopic Submucosal Dissection in North America: A Large Prospective Multicenter Study. *Gastroenterology* 2021; **160**: 2317-2327.e2 [PMID: 33610532 DOI: 10.1053/j.gastro.2021.02.036]
4 **Yang DH**, Kwak MS, Park SH, Ye BD, Byeon JS, Myung SJ, Yang SK, Kim HG, Friedland S. Endoscopic Mucosal Resection with Circumferential Mucosal Incision for Colorectal Neoplasms: Comparison with Endoscopic Submucosal Dissection and between Two Endoscopists with Different Experiences. *Clin Endosc* 2017; **50**: 379-387 [PMID: 28264251 DOI: 10.5946/ce.2016.058]
5 **Sano Y**, Tanaka S, Kudo SE, Saito S, Matsuda T, Wada Y, Fujii T, Ikematsu H, Uraoka T, Kobayashi N, Nakamura H, Hotta K, Horimatsu T, Sakamoto N, Fu KI, Tsuruta O, Kawano H, Kashida H, Takeuchi Y, Machida H, Kusaka T, Yoshida N, Hirata I, Terai T, Yamano HO, Kaneko K, Nakajima T, Sakamoto T, Yamaguchi Y, Tamai N, Nakano N, Hayashi N, Oka S, Iwatate M, Ishikawa H, Murakami Y, Yoshida S, Saito Y. Narrow-band imaging (NBI) magnifying endoscopic classification of colorectal tumors proposed by the Japan NBI Expert Team. *Dig Endosc* 2016; **28**: 526-533 [PMID: 26927367 DOI: 10.1111/den.12644]
6 The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003; **58**: S3-43 [PMID: 14652541 DOI: 10.1016/s0016-5107(03)02159-x]
7 **Inoue T**, Nakagawa K, Yamasaki Y, Shichijo S, Kanesaka T, Maekawa A, Higashino K, Uedo N, Ishihara R, Takeuchi Y. Underwater endoscopic mucosal resection versus endoscopic submucosal dissection for 20-30 mm colorectal polyps. *J Gastroenterol Hepatol* 2021; **36**: 2549-2557 [PMID: 33724540 DOI: 10.1111/jgh.15494]
8 **Tanaka S**, Kashida H, Saito Y, Yahagi N, Yamano H, Saito S, Hisabe T, Yao T, Watanabe M, Yoshida M, Saitoh Y, Tsuruta O, Sugihara KI, Igarashi M, Toyonaga T, Ajioka Y, Kusunoki M, Koike K, Fujimoto K, Tajiri H. Japan Gastroenterological Endoscopy Society guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. *Dig Endosc* 2020; **32**: 219-239 [PMID: 31566804 DOI: 10.1111/den.13545]

9 **Lim XC**, Nistala KRY, Ng CH, Lin SY, Tan DJH, Ho KY, Chong CS, Muthiah M. Endoscopic submucosal dissection vs endoscopic mucosal resection for colorectal polyps: A meta-analysis and meta-regression with single arm analysis. *World J Gastroenterol* 2021; **27**: 3925-3939 [PMID: 34321855 DOI: 10.3748/wjg.v27.i25.3925]

10 **Jacques J**, Wallenhorst T, Chevaux JB, Lépilliez DV, Chaussade S, Rivory J, Legros R, Schaefer M, Leblanc S, Rostain F, Barret M, Belle A, Crepin S, Magne J, Albouys J, Preux PM, Lepetit H, Dahan M, Ponchon T, Pioche M. Endoscopic submucosal dissection (ESD) vs piece-meal endoscopic mucosal resection (PM-EMR) for large laterally spreading lesions: French randomized controlled trial RESECT-COLON (Abstract). *Gastrointest Endosc* 2022; **95** Suppl 6 [DOI: 10.1016/j.gie.2022.04.384]

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2023 June 16; 15(6): 469-479

DOI: 10.4253/wjge.v15.i6.469

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Endoscopic sleeve gastroplasty in class III obesity: Efficacy, safety, and durability outcomes in 404 consecutive patients

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Liu D, China; Zhang J, China

Received: March 6, 2023
Peer-review started: March 6, 2023
First decision: April 28, 2023
Revised: May 8, 2023
Accepted: May 22, 2023
Article in press: May 22, 2023
Published online: June 16, 2023

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Abstract

BACKGROUND

Endoscopic sleeve gastroplasty (ESG) is an effective therapy for class I-II obesity, but there are knowledge gaps in the published literature about its implementation in patients with class III obesity [body mass index (BMI) ≥ 40 kg/m^2].

AIM

To evaluate the safety, clinical efficacy, and durability of ESG in adults with class III obesity.

METHODS

This was a retrospective cohort study that used prospectively collected data on adults with BMI ≥ 40 kg/m^2 who underwent ESG and longitudinal lifestyle counseling at two centers with expertise in endobariatric therapies from May 2018-March 2022. The primary outcome was total body weight loss (TBWL) at 12 mo. Secondary outcomes included changes in TBWL, excess weight loss (EWL) and BMI at various time points up to 36 mo, clinical responder rates at 12 and 24 mo, and comorbidity improvement. Safety outcomes were reported through the

study duration. One-way ANOVA test was performed with multiple Tukey pairwise comparisons for TBWL, EWL, and BMI over the study duration.

RESULTS

404 consecutive patients (78.5% female, mean age 42.9 years, mean BMI 44.8 ± 4.7 kg/m^2) were enrolled. ESGs were performed using an average of 7 sutures, over 42 ± 9 min, and with 100% technical success. TBWL was 20.9 ± 6.2% at 12 mo, 20.5 ± 6.9% at 24 mo, and 20.3 ± 9.5% at 36 mo. EWL was 49.6 ± 15.1% at 12 mo, 49.4 ± 16.7% at 24 mo, and 47.1 ± 23.5% at 36 mo. There was no difference in TBWL at 12, 15, 24, and 36 mo from ESG. TBWL exceeding 10%, 15%, and 20% was achieved by 96.7%, 87.4%, and 55.6% of the cohort at 12 mo, respectively. Of the cohort with the relevant comorbidity at time of ESG, 66.1% had improvement in hypertension, 61.7% had improvement in type II diabetes, and 45.1% had improvement in hyperlipidemia over study duration. There was one instance of dehydration requiring hospitalization (0.2% serious adverse event rate).

CONCLUSION

When combined with longitudinal nutritional support, ESG induces effective and durable weight loss in adults with class III obesity, with improvement in comorbidities and an acceptable safety profile.

Key Words: Endoscopic sleeve gastroplasty; Obesity; Bariatric; Endobariatrics; Class III obesity; Comorbidities

Core Tip: Patients with obesity wishing to avoid bariatric surgery can benefit from endoscopic sleeve gastroplasty (ESG), but little has been published about the safety and efficacy of ESG in those with class III obesity (body mass index ≥ 40 kg/m^2). Based on this appraisal of a large, international cohort, ESG can be safely performed in adults with class III obesity, with clinically meaningful weight loss at one year that can be maintained over the subsequent two years, as well as improvement in weight-related comorbidities. Patients and medical providers should be made aware that ESG combined with longitudinal nutritional support is a promising weight loss tool for those with class III obesity.

Citation: Maselli DB, Hoff AC, Kucera A, Weaver E, Sebring L, Gooch L, Walton K, Lee D, Cratty T, Beal S, Nanduri S, Rease K, Gainey CS, Eaton L, Coan B, McGowan CE. Endoscopic sleeve gastroplasty in class III obesity: Efficacy, safety, and durability outcomes in 404 consecutive patients. *World J Gastrointest Endosc* 2023; 15(6): 469-479

URL: https://www.wjgnet.com/1948-5190/full/v15/i6/469.htm

DOI: https://dx.doi.org/10.4253/wjge.v15.i6.469

INTRODUCTION

Obesity is a chronic, progressive, multifactorial disease spectrum of excess adiposity with detrimental effects on patients' health and well-being[1]. Those with class III obesity [body mass index (BMI) ≥ 40 kg/m^2] have 1.5 times greater risk of all-cause mortality than those with class I (BMI 30.0-34.9 kg/m^2) or class II (BMI 35.0-39.9 kg/m^2) obesity, and compared to individuals of normal weight, they have over double the risk of all-cause mortality, with a loss of 7-14 years of life expectancy[2,3]. While adults with class III obesity account for nearly 6% of the United States adult population, they constitute one-fifth of per-capita healthcare expenditures and thus represent a population in need of effective and safe weight loss strategies[4,5].

Bariatric and metabolic surgeries are the most effective weight loss interventions for patients with obesity[6]. However, the reach of these surgeries is constrained by a variety of barriers, most notably patient perception of risks and desire to avoid invasive procedures; accordingly, only 1% or less of eligible patients pursue bariatric surgery[7,8]. For patients with class III obesity, this rate is estimated to be 1 in 400[9]. Failure to provide such patients with effective surgical weight loss has been linked to development of additional obesity-associated medical problems[10]. These challenges widen the treatment gap in the global burden of obesity, especially among those at the high ranges of BMI.

Over the past decade, endoscopic bariatric therapies have entered the therapeutic landscape, hypothesized to have greater patient acceptance due to their minimally invasive, anatomy-preserving

nature[11]. The endoscopic sleeve gastroplasty (ESG) involves incisionless, per-oral gastric remodeling *via* full thickness sutures placed along the stomach's greater curvature to create a sleeve-like configuration that reduces stomach volume by 80%[12]. It has shown considerable promise in those with class I and II obesity, inducing a total body weight loss of approximately 16% at one year[13,14].

In July 2022, the United States Food and Drug Administration (FDA) granted De Novo Market Authorization for the creation of the ESG using the Apollo ESG™ (formerly OverStitch device, Apollo Endosurgery, Austin, TX, United States) for treatment of obesity in those with BMI from 30 kg/m^2 to 50 kg/m^2. However, due to the relatively recent emergence of endoscopic bariatric therapies, as well as preceding expert level recommendations that they be employed in lower classes of obesity, little has been published on the use of ESG in class III obesity[11,15]. A retrospective review that included 146 adults with class III obesity who underwent ESG at a single center in Spain observed similar weight loss and adverse event outcomes as subjects with class I and II obesity, suggesting ESG is an appropriate therapy in patients with BMIs exceeding 40 kg/m^2, but further study is required to validate the findings to bolster confidence in widespread clinical adoption[16].

To address this, we examined weight loss and safety outcomes up to three years in 404 consecutive patients with class III obesity who underwent ESG, without concomitant weight loss medications, at two centers with expertise in endoscopic bariatric therapies. We hypothesized that ESG in subjects with class III obesity would achieve clinically significant weight loss with an acceptable safety profile.

MATERIALS AND METHODS

Trial design

This was an international, multicenter, retrospective analysis of prospectively followed consecutive patients with class III obesity who underwent ESG. This study was approved by an Institutional Review Board (WCG IRB, Puyallup, WA). The study was conducted following ethical principles outlined in the Declaration of Helsinki and was consistent with the Good Clinical Practices recommendation. All authors had access to the study data and reviewed and approved the final manuscript.

Study population

Study participants were enrolled if they were ≥ 20 years of age, had BMI ≥ 40 kg/m^2, had failed to lose weight through diet/exercise alone, were interested in an endobariatric procedure for weight loss, could provide informed consent, and were willing to comply with a structured lifestyle program and dietary modification. Subjects were excluded for concomitant use of weight loss medications, prior bariatric surgery (except for history of laparoscopic adjusted gastric band status post removal), bleeding disorder or coagulopathy, non-steroidal anti-inflammatory drug dependence, poorly controlled diabetes, and severe cardiopulmonary disease, as well as if hiatal hernia > 4 cm, and/or active peptic ulcer disease was noted at time of ESG.

ESG Procedure and follow up

All subjects underwent self-financed ESGs between May 2018 and March 2022 at True You Weight Loss (Cary, NC, United States) and Clinica Angioskope (Sao Paulo, Brazil). All ESGs were performed by two providers with expertise in endoscopic bariatric therapies, each having performed over five hundred ESG procedures by the start of the study (CM and AH). Procedures were performed using the OverStitch Endoscopic Suturing System (Apollo Endosurgery, Austin, TX, United States) under general anesthesia with endotracheal intubation. Procedural technique was performed as previously published [17]. Subjects were discharged the same day. After the procedure, all patients were enrolled in a comprehensive lifestyle program with long-term nutritional support and monitoring at monthly virtual or in-person visits with registered dieticians who provided counseling on dietary and exercise behaviors to reinforce weight loss. Follow up with a physician or nurse practitioner was also offered as needed during the first year after ESG to provide further support and address symptoms. Patient weights were collected at each visit, either in person or virtually by standardized Bluetooth-enabled digital scale, while safety outcomes were monitored longitudinally.

Study endpoints

The primary outcome of the study was total body weight loss (TBWL) at 12 mo, expressed as a percentage of weight lost in comparison to baseline weight on the day of the ESG procedure. The expectation was that the mean TBWL was at least 10%, which is the expected TBWL following an endobariatric procedure[11]. Secondary endpoints included TBWL at 3, 6, 15, 24, and 36 mo; clinical responder rates (defined as ≥ 10% TBWL, ≥ 15% TBWL, ≥ 20% TBWL, ≥ 25% TBWL, and ≥ 30% TBWL) at 12 and 24 mo; excess weight loss (EWL) and BMI at 3, 6, 12, 15, 24, and 36 mo; number of sutures used to create the ESG; and technical success (defined as completed procedure without early termination due to technical challenges or complications), as reported in similar studies of ESG[18]. The presence of hypertension, type II diabetes, and hyperlipidemia at time of ESG was defined as any of the following:

Established diagnosis by a primary or referring provider; use of medication/devices to treat the condition. Additionally, type II diabetes was diagnosed if hemoglobin A1c ≥ 6.5% within 3 mo prior to ESG, and hyperlipidemia was diagnosed if low-density lipoprotein ≥ 160 mg/dL or total cholesterol ≥ 200 mg/dL within 3 mo of ESG. Improvement in comorbidity was defined as reduction in or complete discontinuation of medications used to treat the condition by a referring provider at any point in time during study duration. It was not standard practice to repeat laboratory values after ESG in our centers, but improvement in comorbidity was also reported if a patient obtained labs elsewhere that showed hemoglobin A1c < 6.5% (type II diabetes), total cholesterol < 200 mg/dL (hyperlipidemia), and/or low-density lipoprotein < 160 mg/dL (hyperlipidemia) at any point in time during study duration. Safety data were collected throughout the three-year study duration and were graded according to the American Society for Gastrointestinal Endoscopy lexicon[19].

Statistical analysis and data representation

The statistical components of this study were performed and reviewed by a biomedical statistician. Descriptive statistics were used for analyses. All data were tested for normality using the Kolmogorov-Smirnov test, Q-Q plot, and Levene's test. Continuous variables were expressed as means with standard deviations or medians with ranges and 95% confidence intervals. One-way ANOVA test was performed with multiple Tukey pairwise comparisons with months from the procedure as the grouping variable for TBWL, EWL, and BMI. Categorical variables were expressed as frequencies. The Kruskal-Wallis test was performed to evaluate differences in clinical responder rates with months from procedure as the grouping variable. This test was only performed for 10% and 20% clinical responders. If a difference was detected, then Wilcoxan Rank Sum test with Bonferroni Correction was performed to determine comparisons with significant differences in clinical responders. Follow up was reported as a percentage, calculated as number of patients with available data at a time point, divided by number of patients expected to have available data at that time point. Adverse event rate frequency was based on the number of patients treated. P values < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS (version 29.0).

RESULTS

Four hundred and four patients (mean age 42.9 years, 78.5% female, mean pre-procedural weight 127.3 ± 20.1 kg, mean pre-procedural BMI 44.8 ± 4.7 kg/m^2) underwent ESG between May 2018 and March 2022. Technical success rate was 100%. Mean procedure duration was 42 ± 9 min and used a median of 7 sutures, with a range of 4 to 12 sutures. Prior to ESG, the cohort had the following obesity-associated comorbidities: Hypertension (35.4%), type II diabetes (17.8%), and hyperlipidemia (16.8%). Table 1 shows the baseline demographic and anthropometric characteristics of the study cohort.

Clinical outcomes

Table 2 shows subject accountability by visit, with greater than 80% follow-up achieved at all time points. TBWL was 12.5 ± 3.7% at 3 mo, 16.5 ± 4.8% at 6 mo, 20.9 ± 6.2% at 12 mo, 21.6 ± 7.2% at 15 mo, 20.5 ± 6.9% at 24 mo, and 20.3 ± 9.5% at 36 mo (Figure 1A). EWL was 29.5 ± 9.6% at 3 mo, 39.2 ± 12.7% at 6 mo, 49.6 ± 15.1% at 12 mo, 51.6 ± 16.8% at 15 mo, 49.4 ± 16.7% at 24 mo, and 47.1 ± 23.5% at 36 mo (Figure 1B). BMI decreased from 44.8 ± 4.7 kg/m^2 at baseline to 38.8 ± 3.1 kg/m^2 at 3 mo, 37.0 ± 4.0 kg/m^2 at 6 mo, 35.0 ± 4.0 kg/m^2 at 12 mo, 34.5 ± 4.7 kg/m^2 at 15 mo, 34.0 ± 4.7 kg/m^2 at 24 mo, and 35.6 ± 5.5 kg/m^2 at 36 mo (Figure 1C). One-way ANOVA results for TBWL and EWL revealed statistically significant differences in values between preceding and subsequent timepoints through month 12, with no differences noted between 12, 15, 24, and 36 mo. For BMI, there were statistically significant differences in values between preceding and subsequent time points through month 6, with no statistical differences noted from time points spanning 6 to 36 mo. Figure 2 illustrates the distribution of obesity classes during the study. While less than 10% of subjects were cured of obesity during study duration, most subjects (85.4%) exited class III obesity by 6 mo, without notable increase in the proportion of class III obesity in the study duration. A plurality of the cohort had class I obesity by 12 and 24 mo. 12-mo clinical response rates showed 96.7% achieved at least 10% TBWL, 87.4% achieved at least 15% TBWL, and 55.6% achieved at least 20% TBWL, with similar proportions of clinical responders observed at 24 mo (Figure 3). Kruskal-Wallis confirmed no difference in ≥ 10% TBWL rates at 12 *vs* 24 mo or ≥ 20% TBWL rates at 12 *vs* 24 mo (P < 0.001 for both). Of the cohort with the respective comorbidity at the time of ESG, 66.1% had improvement in hypertension, 61.7% had improvement in type II diabetes, and 45.1% had improvement in hyperlipidemia over study duration. No patient underwent an additional endoscopic procedure for repeat suturing. One subject (starting BMI 50.5 kg/m^2) converted to a Roux-en-Y gastric bypass at 22 mo after achieving 22% TBWL.

Safety outcomes

There were no instances of death, gastrointestinal perforation, abscess/sepsis, gastrointestinal bleeding, intensive care unit admission, or need for endoscopic or surgical intervention for management of

Table 1 Baseline demographic and anthropometric characteristics

Characteristic	Value
Age (yr)	42.9 ± 9.4
% Female	78.5
Weight (kg)	127.3 ± 20.1
BMI (kg/m^2)	44.8 ± 4.7
Comorbidities, *n* (%)	
Hypertension	143 (35.4%)
Type II diabetes	72 (17.8%)
Hyperlipidemia	68 (16.8%)

BMI: Body mass index.

Table 2 Subject accountability by visit

	3 mo	6 mo	12 mo	15 mo	24 mo	36 mo
Total cohort	404	404	404	404	404	404
Not yet out of window	52	122	217	266	309	387
Expected[1]	352	282	187	138	95	17
Actual	312	233	151	112	82	15
% Follow-up	88.60%	82.60%	80.70%	81.20%	86.30%	88.30%

[1]Expected = Total Cohort – Not Yet Out of Window, % Follow up = Actual/Expected × 100.

procedural complications. There were two instances of dehydration requiring emergency room presentation 2 d and 8 d after the ESG, one of which required 3-day hospitalization for acute kidney injury, which resolved with intravenous fluids. This yielded an overall adverse event rate of 0.5% and a 0.2% serious adverse event (SAE) rate.

DISCUSSION

This is one of the first studies—and the largest to date—that examines the novel application of ESG in patients with class III obesity, a demographic traditionally relegated to surgery for weight loss. The data presented here help address misperceptions about ESG in patients with class III obesity that ostensibly are founded on concerns about insufficient efficacy, increased risk of adverse outcomes, and technical challenges in a high BMI population. Crucially, these findings support the United States FDA's recent authorization for use of the ESG in patients with obesity with BMI spanning 30 kg/m^2 to 50 kg/m^2.

This study demonstrates that ESG, without concomitant weight loss medications, and in conjunction with prescribed diet/exercise counseling, can induce clinically significant weight loss in patients with BMI ≥ 40 kg/m^2. Our cohort achieved a TBWL of nearly 21% at 12 mo, exceeding the 16% TBWL reported in multiple meta-analyses of ESG, and which was sustained at years 2 and 3[13,14,20]. Our results were concordant with a recently published study by Lopez-Nava *et al*[16] in which 146 subjects with class III obesity achieved 20.5% TBWL at one year. Weight loss appears to be most pronounced in year one after ESG, with efforts later focused on weight loss maintenance in years two and three, in line with the weight loss trajectory from ESG previously observed by Sharaiha and colleagues[21].

An important finding in our study is that most patients with class III obesity who undergo ESG will exit class III obesity by 6 mo and further improve their weight at 12 mo. Compellingly, very few subjects return to class III obesity at years 2 and 3. However, while weight loss was clinically significant, very few in the cohort were cured of obesity during the duration of the study. This underscores the challenges of managing a chronic, progressive, relapsing disorder and may provide the rationale for concomitant or sequential treatment with weight loss medications in this patient population to achieve even greater weight loss; in fact, early success with incretin-based pharmacotherapy and ESG has been reported[22]. This observation additionally supports the concept of ESG as a bridging procedure in

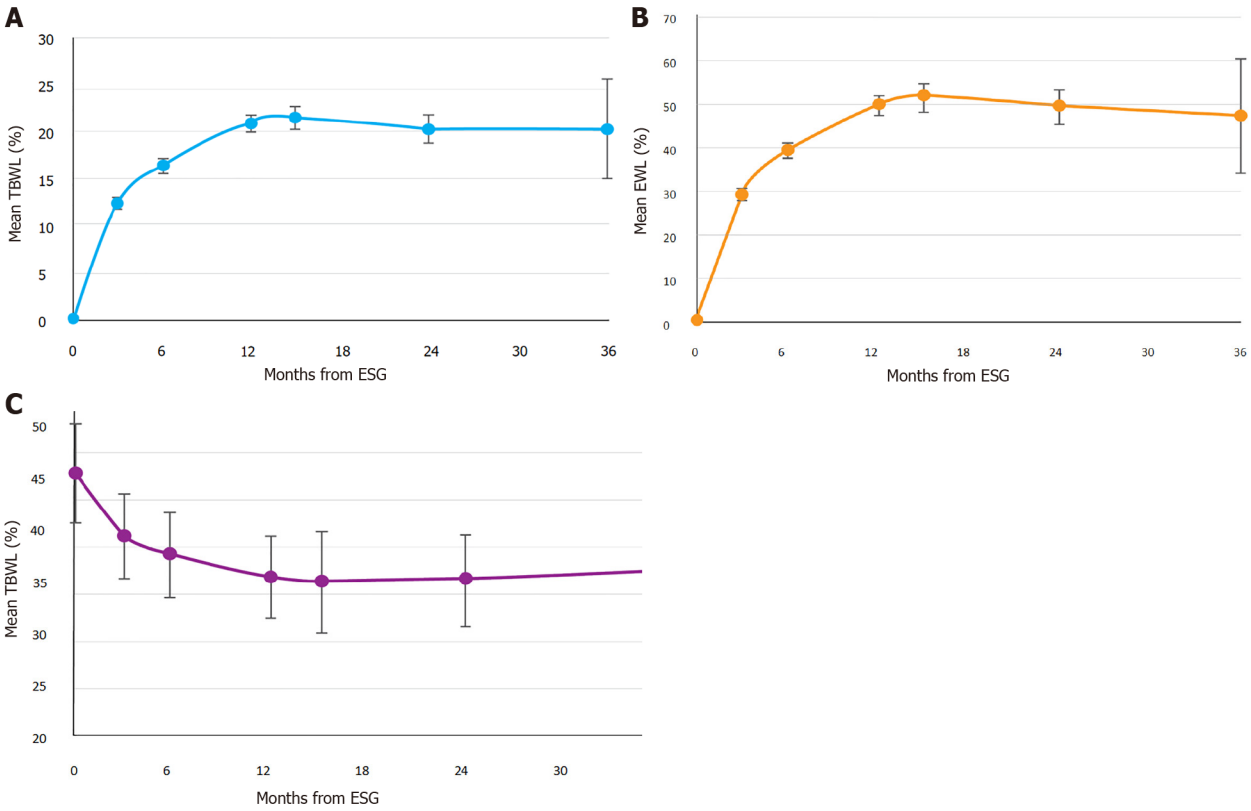

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Figure 1 Effect of endoscopic sleeve gastroplasty in adults with class III obesity over 3 years. A: Total body weight loss over study duration; B: Excess weight loss over study duration; C: Body mass index over study duration. ESG: Endoscopic sleeve gastroplasty; TBWL: Total body weight loss; EWL: Excess weight loss.

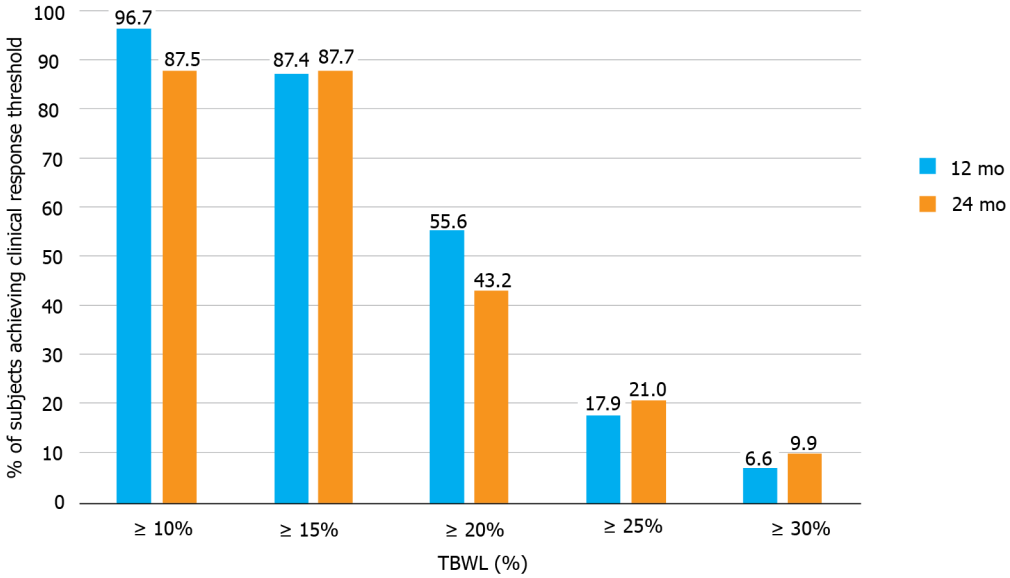

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Figure 2 Clinical response ratesin adults with class III obesity after endoscopic sleeve gastroplasty. TBWL: Total body weight loss.

patients with markedly elevated BMI but with surgical contraindications or elevated operative risk, as has been published in a small case series by Zorron and colleagues, with a subsequent larger cohort showing safe revision of ESG to laparoscopic sleeve gastrectomy (LSG) by Alqahtani and colleagues[23,24]. Ultimately, the clinical response to ESG in our cohort remains substantive, particularly given that traditional bariatric surgeries have a limited penetrance for eligible patients, and ESG provides a minimally invasive alternative for those who are not interested in pursuing surgical weight loss[7,8].

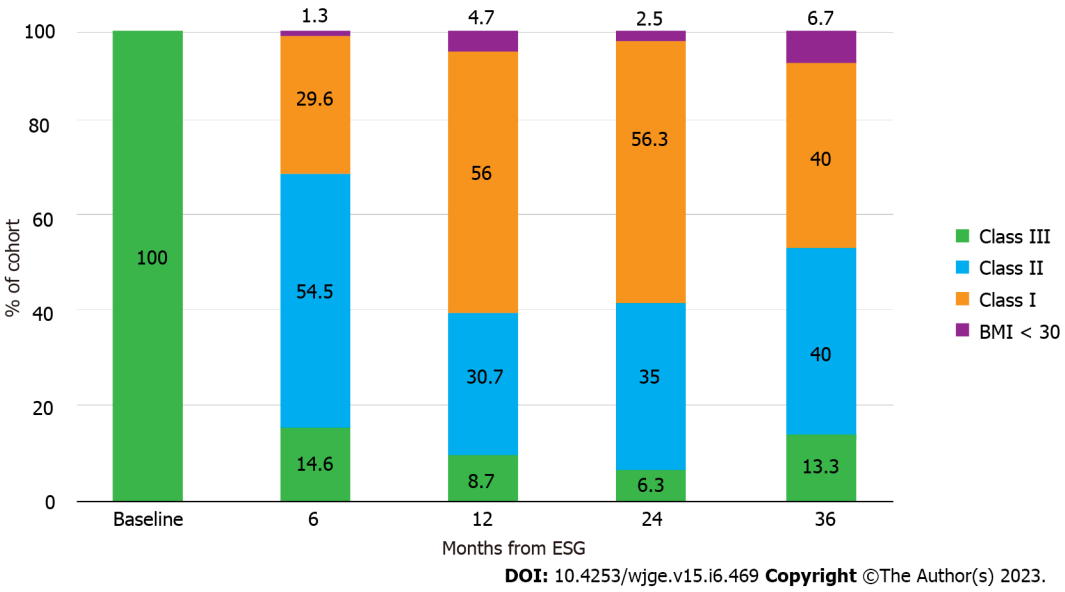

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Figure 3 Distribution of obesity classes over 3 years after endoscopic sleeve gastroplasty in adults with class III obesity. TBWL: Total body weight loss; BMI: Body mass index.

The Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) thresholds recommend that an endoscopic bariatric and metabolic therapy facilitate at least 25% EWL at 12 mo[25]. In this cohort, EWL was nearly double this threshold, at almost 50% at 12 and 24 mo. This is less than the approximately 60% 12-mo EWL reported in meta-analyses of ESG, but most subjects in the ESG literature were closer to ideal body weight, which augments EWL for a given magnitude of weight loss [13,14,26]. The EWL of our cohort fell short of EWL observed following LSG, which is approximately 86% at one year; however, this does diminish to around 63% at 3 years[27]. A recently published study comparing ESG and LSG, in which ESG subjects had a baseline BMI of 32.5 ± 3.1 kg/m^2, showed a mean difference in TBWL of 9.7% at 1 year and 4.8% at 3 years in favor of LSG[28]. While both interventions create a narrowed, restricted gastric reservoir, this discrepancy may result from differences in hormonal influences (LSG involves resection of the fundus and thus diminishes ghrelin, whereas ESG does not) and distinct foregut sensorimotor effects (LSG accelerates gastric emptying to impact proximal small intestine-mediated satiation pathways, where ESG delays gastric emptying to impact gastric-mediated peripheral appetite signals)[29-32]. Further exploration of weight loss and safety outcomes in ESG *vs* LSG warrant direct head-to-head trials, primarily to better inform patients of their available options and the differences between current surgical and endoscopic bariatric therapies.

As approximately 75% of adults with class III obesity have at least one obesity-associated comorbidity, improvement in comorbidities is a valuable measure[25]. Throughout the study duration, comorbidity improvement was observed in over half of those with hypertension and type II diabetes, and nearly half of those with hyperlipidemia. We attribute this phenomenon to clinical responder rates, as almost all subjects achieved at least 10% TBWL at one year. This appears to be a meaningful inflection point for improvement in obesity-related comorbidities[26]. This phenomenon may help reduce the side effects, interactions, and cost associated with comorbidity-related polypharmacy often observed in patients with class III obesity.

Performance of the ESG in patients with BMI ≥ 40 kg/m^2 demonstrates an acceptable safety profile for clinical adoption, with an observed 0.2% SAE rate that is in line with the expert consensus that an endoscopic bariatric and metabolic therapy not have a SAE rate exceeding 5%[25]. The majority of severe SAEs from ESG—particularly the accounts of gastric perforation, fluid collection/abscess, venous thromboembolism, and gastrointestinal bleeding reported in the literature—are expected to occur within the first month after the ESG, and thus our inclusion of all 404 patients permitted a suitable and robust ability to capture these outcomes[26]. Both adverse events in this study were graded as mild in severity according to the lexicon[19]. We suspect that these favorable safety outcomes stem from a variety of factors: performance of ESG by highly experienced endobariatric physicians; procedural technique that maintains full-thickness tissue acquisition while avoiding extra-gastric structures; avoidance of the thin-walled gastric fundus; regular follow-up visits and physician contact for symptom assessment; and exclusion of patients with severe systemic disease.

While the safety profile of ESG in patients with class III obesity is appealing compared to that of bariatric surgery, ambitions of narrowing the management gap in class III obesity with the ESG are tempered by barriers more unique to endoscopic bariatric therapies[33]. Despite the recent United States FDA authorization, the ESG is not covered by most insurances. This puts a financial burden on patients

as they navigate a cash pay model. Moreover, the technical implementation of ESG remains heterogenous, and while dedicated training programs exist for bariatric surgeries, there are ongoing discussions about how best to develop and standardize endobariatric training programs and establish credentialing requirements for interested endoscopists[34]. Thus, while demonstrating favorable efficacy, safety, and acceptance, ESG still faces practical challenges that must be addressed for successful clinical adoption.

From a technical standpoint, there was little difference between creation of ESGs in our subjects with class III obesity and our patients with class I and II obesity. Patients required a median of 7 sutures, which is typical for our ESGs in lower classes of obesity, and our suture pattern was not modified for this patient population. While same-day discharge was feasible for all subjects in this cohort, there are still precautions regarding anesthesia risk, airway management, and equipment and facility factors that have to be considered by institutions aiming to offer ESG in this patient population.

Our study has several strengths. The cohort is the largest studied to date and was derived from two high-volume, experienced endobariatric centers that utilize the same procedural technique and aftercare protocols. Both study endoscopists are highly trained, having performed more than 3500 combined ESG procedures, reducing the impact of technical variability and inexperience. Finally, nutritional support with dieticians at both centers was comprehensive, and follow-up was near-complete, despite the impact of the coronavirus disease 2019 (COVID-19) pandemic.

This study also had certain limitations. Regarding trial design, this was a retrospective review of subjects that lacked a comparator arm, so the true difference in weight loss outcomes relative to a similar population using diet and exercise for weight loss is not known; however, all patients treated at both centers had failed to lose weight or maintain prior weight loss by the time they sought ESG. Second, the prevalence of medical comorbidities in this cohort was lower than would be expected for class III obesity. This may have been because diagnosis of comorbidities relied largely on indirect report from primary care physicians and patients or medication lists rather than direct lab measurement in all instances, and comorbidity improvement was limited insofar as post-ESG lab values were not widely available given that this is not standard practice in our centers. Nevertheless, this cohort was, in essence, a "healthy" population of patients with class III obesity, which is not unusual for those seeking non-surgical treatment but may have led to an under-assessment of metabolic impacts. Third, the external validity of this study may be limited considering the high level of experience of the involved centers, both in terms of procedural volume and longitudinal aftercare capabilities. Additionally, 281 (69%) of the 404 patients had their ESG procedure within 6-months of the onset of the COVID-19 pandemic, which may have impacted their overall weight loss. Finally, though patient adherence throughout the study duration was greater than 80%, the absolute number of subjects who reached the 24- and 36-month timepoints was small, meaning we must be cautious when interpreting these later outcomes.

Based on the promising results presented in this study, ESG in combination with a prescribed nutritional program should be offered to patients with class III obesity. Given the global burden of obesity, compounded by limited therapeutic options that are both accessible and appealing to patients, ESG can be a useful tool for reducing the substantial management gap in this disease when performed by experienced endobariatric physicians with reliable, long-term aftercare. Further study of ESG in class III obesity should assess improvement in associated medical problems, the effects of combination ESG-pharmacotherapy, and directly compare ESG to traditional bariatric surgeries.

CONCLUSION

When combined with longitudinal nutritional support, ESG is a safe and effective tool for adults with class III obesity, with clinically-meaningfully weight loss at one year that was sustained in the subsequent two years, as well as improvement in weight-related comorbidities. Patients may need additional therapy to reduce body mass index out of obesity range.

ARTICLE HIGHLIGHTS

Research background

Endoscopic sleeve gastroplasty (ESG) is a minimally invasive weight loss tool that narrows and shortens the stomach into a tubular construct through full-thickness suturing. The majority of published data on the ESG focus on patients with class I [(Body mass index (BMI) 30.0-34.9 kg/m^2] or class II (BMI 35.0-39.9 kg/m^2) obesity.

Research motivation

Patients with class III obesity (BMI ≥ 40 kg/m^2) face greater mortality risk and increased emergence of weight-related comorbidities compared those of lower obesity classes; however, the vast majority of patients with class III obesity do not pursue bariatric and metabolic surgery, leading to a substantial

therapeutic gap in this patient population, which ESG may help address.

Research objectives

To address knowledge gaps in the clinical adoption of ESG as a weight loss tool in adults at higher ranges of body mass index, we sought to evaluate the clinical efficacy of ESG in patients with class III obesity based on weight loss and resolution of comorbidities, as well as safety outcomes, over the course of three years.

Research methods

This was a retrospective evaluation of prospective collected data of adult patients undergoing ESG from May 2018-March 2022 at two centers with expertise in endobariatric therapies.

Research results

404 adult patients with class III obesity underwent ESG and achieved 20.9 ± 6.2% total body weight loss and 49.6 ± 15.1% excess weight loss at one year, which was maintained at two and three years. 87.4% of patients achieved > 15% total body weight loss by one year. Of the cohort, 66.1% had improvement in hypertension, 61.7% had improvement in type II diabetes, and 45.1% had improvement in hyperlipidemia over the study duration. There was a 0.2% serious adverse event rate.

Research conclusions

When combined with longitudinal nutritional support, ESG facilitates safe and effective weight loss at one year in adults with class III obesity, which is maintained at years two and three. ESG should be considered for patients with class III obesity wishing to avoid metabolic and bariatric surgery.

Research perspectives

While safe and effective in the treatment of class III obesity, ESG did not cure patients of obesity within the confines of this study, and future research should evaluate practices that enhance weight loss from ESG in this population, including procedural modifications or combination therapy with pharmacologic agents.

FOOTNOTES

Author contributions: Maselli DB prepared and edited the manuscript; Hoff AC, Weaver E, Sebring L, Gooch L, Walton K, collected data and critically revised the manuscript; Kucera A, critically revised the manuscript and authored the study protocol; Lee D critically revised the manuscript and managed the study database; Cratty T, Beal S, Nanduri S, Rease K, Gainey C, and Coan B critically revised the manuscript; McGowan CE conceptualized and designed the study and critically revised the manuscript.

Institutional review board statement: The study was reviewed and approved for publication by our Institutional Reviewer (WCG IRB, Puyallup, WA).

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrollment as part of undergoing the ESG at the institutions participating in this study.

Conflict-of-interest statement: All the Authors have no conflict of interest related to the manuscript except as specified below: Christopher E. McGowan: consultant for Apollo Endosurgery. Anna C. Hoff: consultant for Apollo Endosurgery. Daniel B. Maselli: consultant for Apollo Endosurgery. No author has a proprietary relationship in Apollo Endosurgery.

Data sharing statement: The original anonymous dataset is available on request from the corresponding author at drmcgowan@trueyouweightloss.com.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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S-Editor: Ma YJ
L-Editor: A
P-Editor: Ma YJ

REFERENCES

1 **Bray GA**, Kim KK, Wilding JPH; World Obesity Federation. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. *Obes Rev* 2017; **18**: 715-723 [PMID: 28489290 DOI: 10.1111/obr.12551]

2 **Kitahara CM**, Flint AJ, Berrington de Gonzalez A, Bernstein L, Brotzman M, MacInnis RJ, Moore SC, Robien K, Rosenberg PS, Singh PN, Weiderpass E, Adami HO, Anton-Culver H, Ballard-Barbash R, Buring JE, Freedman DM, Fraser GE, Beane Freeman LE, Gapstur SM, Gaziano JM, Giles GG, Håkansson N, Hoppin JA, Hu FB, Koenig K, Linet MS, Park Y, Patel AV, Purdue MP, Schairer C, Sesso HD, Visvanathan K, White E, Wolk A, Zeleniuch-Jacquotte A, Hartge P. Association between class III obesity (BMI of 40-59 kg/m^2) and mortality: a pooled analysis of 20 prospective studies. *PLoS Med* 2014; **11**: e1001673 [PMID: 25003901 DOI: 10.1371/journal.pmed.1001673]

3 **Global BMI Mortality Collaboration**, Di Angelantonio E, Bhupathiraju ShN, Wormser D, Gao P, Kaptoge S, Berrington de Gonzalez A, Cairns BJ, Huxley R, Jackson ChL, Joshy G, Lewington S, Manson JE, Murphy N, Patel AV, Samet JM, Woodward M, Zheng W, Zhou M, Bansal N, Barricarte A, Carter B, Cerhan JR, Smith GD, Fang X, Franco OH, Green J, Halsey J, Hildebrand JS, Jung KJ, Korda RJ, McLerran DF, Moore SC, O'Keeffe LM, Paige E, Ramond A, Reeves GK, Rolland B, Sacerdote C, Sattar N, Sofianopoulou E, Stevens J, Thun M, Ueshima H, Yang L, Yun YD, Willeit P, Banks E, Beral V, Chen Zh, Gapstur SM, Gunter MJ, Hartge P, Jee SH, Lam TH, Peto R, Potter JD, Willett WC, Thompson SG, Danesh J, Hu FB. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet* 2016; **388**: 776-786 [PMID: 27423262 DOI: 10.1016/S0140-6736(16)30175-1]

4 **Flegal KM**, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. *JAMA* 2010; **303**: 235-241 [PMID: 20071471 DOI: 10.1001/jama.2009.2014]

5 **Arterburn DE**, Maciejewski ML, Tsevat J. Impact of morbid obesity on medical expenditures in adults. *Int J Obes (Lond)* 2005; **29**: 334-339 [PMID: 15685247 DOI: 10.1038/sj.ijo.0802896]

6 **Clinical Guidelines on the Identification**, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. *Obes Res* 1998; **6** Suppl 2: 51S-209S

7 **Imbus JR**, Voils CI, Funk LM. Bariatric surgery barriers: a review using Andersen's Model of Health Services Use. *Surg Obes Relat Dis* 2018; **14**: 404-412 [PMID: 29249585 DOI: 10.1016/j.soard.2017.11.012]

8 **Campos GM**, Khoraki J, Browning MG, Pessoa BM, Mazzini GS, Wolfe L. Changes in Utilization of Bariatric Surgery in the United States From 1993 to 2016. *Ann Surg* 2020; **271**: 201-209 [PMID: 31425292 DOI: 10.1097/SLA.0000000000003554]

9 **Martin M**, Beekley A, Kjorstad R, Sebesta J. Socioeconomic disparities in eligibility and access to bariatric surgery: a national population-based analysis. *Surg Obes Relat Dis* 2010; **6**: 8-15 [PMID: 19782647 DOI: 10.1016/j.soard.2009.07.003]

10 **Al Harakeh AB**, Burkhamer KJ, Kallies KJ, Mathiason MA, Kothari SN. Natural history and metabolic consequences of morbid obesity for patients denied coverage for bariatric surgery. *Surg Obes Relat Dis* 2010; **6**: 591-596 [PMID: 21111379 DOI: 10.1016/j.soard.2010.08.012]

11 **ASGE/ASMBS Task Force on Endoscopic Bariatric Therapy**. A pathway to endoscopic bariatric therapies. *Surg Obes Relat Dis* 2011; **7**: 672-682 [PMID: 22082971 DOI: 10.1016/j.soard.2011.09.008]

12 **Kumar N**, Abu Dayyeh BK, Lopez-Nava Breviere G, Galvao Neto MP, Sahdala NP, Shaikh SN, Hawes RH, Gostout CJ, Goenka MK, Orillac JR, Alvarado A, Jirapinyo P, Zundel N, Thompson CC. Endoscopic sutured gastroplasty: procedure evolution from first-in-man cases through current technique. *Surg Endosc* 2018; **32**: 2159-2164 [PMID: 29075966 DOI: 10.1007/s00464-017-5869-2]

13 **Hedjoudje A**, Abu Dayyeh BK, Cheskin LJ, Adam A, Neto MG, Badurdeen D, Morales JG, Sartoretto A, Nava GL, Vargas E, Sui Z, Fayad L, Farha J, Khashab MA, Kalloo AN, Alqahtani AR, Thompson CC, Kumbhari V. Efficacy and Safety of Endoscopic Sleeve Gastroplasty: A Systematic Review and Meta-Analysis. *Clin Gastroenterol Hepatol* 2020; **18**: 1043-1053.e4 [PMID: 31442601 DOI: 10.1016/j.cgh.2019.08.022]

14 **de Miranda Neto AA**, de Moura DTH, Ribeiro IB, Khan A, Singh S, da Ponte Neto AM, Madruga Neto AC, do Monte Junior ES, Tustumi F, Bernardo WM, de Moura EGH. Efficacy and Safety of Endoscopic Sleeve Gastroplasty at Mid Term in the Management of Overweight and Obese Patients: a Systematic Review and Meta-Analysis. *Obes Surg* 2020; **30**: 1971-1987 [PMID: 32107706 DOI: 10.1007/s11695-020-04449-9]

15 **Neto MG**, Silva LB, de Quadros LG, Grecco E, Filho AC, de Amorim AMB, de Santana MF, Dos Santos NT, de Lima JHF, de Souza TF, de Morais HWP, Vieira FM, Moon R, Teixeira AF; Brazilian Endoscopic Sleeve Gastroplasty Collaborative. Brazilian Consensus on Endoscopic Sleeve Gastroplasty. *Obes Surg* 2021; **31**: 70-78 [PMID: 32815105 DOI: 10.1007/s11695-020-04915-4]

16 **Lopez-Nava G**, Laster J, Negi A, Fook-Chong S, Bautista-Castaño I, Asokkumar R. Endoscopic sleeve gastroplasty (ESG) for morbid obesity: how effective is it? *Surg Endosc* 2022; **36**: 352-360 [PMID: 33492503 DOI:

10.1007/s00464-021-08289-1]
17 **James TW**, Reddy S, Vulpis T, McGowan CE. Endoscopic Sleeve Gastroplasty Is Feasible, Safe, and Effective in a Non-academic Setting: Short-Term Outcomes from a Community Gastroenterology Practice. *Obes Surg* 2020; **30**: 1404-1409 [PMID: 31853865 DOI: 10.1007/s11695-019-04331-3]
18 **Sarkar A**, Tawadros A, Andalib I, Shahid HM, Tyberg A, Alkhiari R, Gaidhane M, Kedia P, John ES, Bushe B, Martinez GM, Zamarripa F, Carames MC, Carames JC, Casarodriguez F, Bove V, Costamagna G, Boskoski I, Kahaleh M. Safety and efficacy of endoscopic sleeve gastroplasty for obesity management in new bariatric endoscopy programs: a multicenter international study. *Ther Adv Gastrointest Endosc* 2022; **15**: 26317745221093883 [PMID: 35694412 DOI: 10.1177/26317745221093883]
19 **Cotton PB**, Eisen GM, Aabakken L, Baron TH, Hutter MM, Jacobson BC, Mergener K, Nemcek A Jr, Petersen BT, Petrini JL, Pike IM, Rabeneck L, Romagnuolo J, Vargo JJ. A lexicon for endoscopic adverse events: report of an ASGE workshop. *Gastrointest Endosc* 2010; **71**: 446-454 [PMID: 20189503 DOI: 10.1016/j.gie.2009.10.027]
20 **Storm AC**, Abu Dayyeh BK. Endoscopic sleeve gastroplasty for obesity: defining the risk and reward after more than 1600 procedures. *Gastrointest Endosc* 2019; **89**: 1139-1140 [PMID: 31104746 DOI: 10.1016/j.gie.2019.02.025]
21 **Sharaiha RZ**, Hajifathalian K, Kumar R, Saunders K, Mehta A, Ang B, Skaf D, Shah S, Herr A, Igel L, Dawod Q, Dawod E, Sampath K, Carr-Locke D, Brown R, Cohen D, Dannenberg AJ, Mahadev S, Shukla A, Aronne LJ. Five-Year Outcomes of Endoscopic Sleeve Gastroplasty for the Treatment of Obesity. *Clin Gastroenterol Hepatol* 2021; **19**: 1051-1057.e2 [PMID: 33011292 DOI: 10.1016/j.cgh.2020.09.055]
22 **Badurdeen D**, Hoff AC, Hedjoudje A, Adam A, Itani MI, Farha J, Abbarh S, Kalloo AN, Khashab MA, Singh VK, Oberbach A, Neto MG, Barrichello S, Kumbhari V. Endoscopic sleeve gastroplasty plus liraglutide *vs* endoscopic sleeve gastroplasty alone for weight loss. *Gastrointest Endosc* 2021; **93**: 1316-1324.e1 [PMID: 33075366 DOI: 10.1016/j.gie.2020.10.016]
23 **Zorron R**, Veltzke-Schlieker W, Adler A, Denecke C, Dziodzio T, Pratschke J, Benzing C. Endoscopic sleeve gastroplasty using Apollo Overstitch as a bridging procedure for superobese and high risk patients. *Endoscopy* 2018; **50**: 81-83 [PMID: 29041019 DOI: 10.1055/s-0043-119685]
24 **Alqahtani AR**, Elahmedi M, Alqahtani YA, Al-Darwish A. Laparoscopic Sleeve Gastrectomy After Endoscopic Sleeve Gastroplasty: Technical Aspects and Short-Term Outcomes. *Obes Surg* 2019; **29**: 3547-3552 [PMID: 31214968 DOI: 10.1007/s11695-019-04024-x]
25 **ASGE Bariatric Endoscopy Task Force and ASGE Technology Committee**, Abu Dayyeh BK, Kumar N, Edmundowicz SA, Jonnalagadda S, Larsen M, Sullivan S, Thompson CC, Banerjee S. ASGE Bariatric Endoscopy Task Force systematic review and meta-analysis assessing the ASGE PIVI thresholds for adopting endoscopic bariatric therapies. *Gastrointest Endosc* 2015; **82**: 425-38.e5 [PMID: 26232362 DOI: 10.1016/j.gie.2015.03.1964]
26 **Singh S**, Hourneaux de Moura DT, Khan A, Bilal M, Ryan MB, Thompson CC. Safety and efficacy of endoscopic sleeve gastroplasty worldwide for treatment of obesity: a systematic review and meta-analysis. *Surg Obes Relat Dis* 2020; **16**: 340-351 [PMID: 31932205 DOI: 10.1016/j.soard.2019.11.012]
27 **Alvarenga ES**, Lo Menzo E, Szomstein S, Rosenthal RJ. Safety and efficacy of 1020 consecutive laparoscopic sleeve gastrectomies performed as a primary treatment modality for morbid obesity. A single-center experience from the metabolic and bariatric surgical accreditation quality and improvement program. *Surg Endosc* 2016; **30**: 2673-2678 [PMID: 26541727 DOI: 10.1007/s00464-015-4548-4]
28 **Alqahtani AR**, Elahmedi M, Aldarwish A, Abdurabu HY, Alqahtani S. Endoscopic gastroplasty *vs* laparoscopic sleeve gastrectomy: a noninferiority propensity score-matched comparative study. *Gastrointest Endosc* 2022; **96**: 44-50 [PMID: 35248571 DOI: 10.1016/j.gie.2022.02.050]
29 **McCarty TR**, Jirapinyo P, Thompson CC. Effect of Sleeve Gastrectomy on Ghrelin, GLP-1, PYY, and GIP Gut Hormones: A Systematic Review and Meta-analysis. *Ann Surg* 2020; **272**: 72-80 [PMID: 31592891 DOI: 10.1097/SLA.0000000000003614]
30 **Lopez-Nava G**, Negi A, Bautista-Castaño I, Rubio MA, Asokkumar R. Gut and Metabolic Hormones Changes After Endoscopic Sleeve Gastroplasty (ESG) Vs. Laparoscopic Sleeve Gastrectomy (LSG). *Obes Surg* 2020; **30**: 2642-2651 [PMID: 32193741 DOI: 10.1007/s11695-020-04541-0]
31 **Rapaka B**, Maselli DB, Lopez-Nava G, Bautista-Castaño I, Matar R, Jaruvongvanich V, Vargas EJ, Storm AC, Acosta A, Abu Dayyeh BK. Effects on physiologic measures of appetite from intragastric balloon and endoscopic sleeve gastroplasty: results of a prospective study. *Chin Med J (Engl)* 2022; **135**: 1234-1241 [PMID: 35788090 DOI: 10.1097/CM9.0000000000002097]
32 **Vargas EJ**, Bazerbachi F, Calderon G, Prokop LJ, Gomez V, Murad MH, Acosta A, Camilleri M, Abu Dayyeh BK. Changes in Time of Gastric Emptying After Surgical and Endoscopic Bariatrics and Weight Loss: A Systematic Review and Meta-Analysis. *Clin Gastroenterol Hepatol* 2020; **18**: 57-68.e5 [PMID: 30954712 DOI: 10.1016/j.cgh.2019.03.047]
33 **Fayad L**, Adam A, Schweitzer M, Cheskin LJ, Ajayi T, Dunlap M, Badurdeen DS, Hill C, Paranji N, Lalezari S, Kalloo AN, Khashab MA, Kumbhari V. Endoscopic sleeve gastroplasty *vs* laparoscopic sleeve gastrectomy: a case-matched study. *Gastrointest Endosc* 2019; **89**: 782-788 [PMID: 30148991 DOI: 10.1016/j.gie.2018.08.030]
34 **Jirapinyo P**, Thompson CC. Training in Bariatric and Metabolic Endoscopic Therapies. *Clin Endosc* 2018; **51**: 430-438 [PMID: 30301319 DOI: 10.5946/ce.2018.148]

World Journal of Gastrointestinal Endoscopy

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World J Gastrointest Endosc 2023 June 16; 15(6): 480-490

DOI: 10.4253/wjge.v15.i6.480

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Study

Prevalence and clinical risk factors for esophageal candidiasis in non-human immunodeficiency virus patients: A multicenter retrospective case-control study

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): E

P-Reviewer: Glumac S, Croatia; Meena DS, India; Sachdeva S, India

Received: April 17, 2023
Peer-review started: April 17, 2023
First decision: May 19, 2023
Revised: May 20, 2023
Accepted: May 31, 2023
Article in press: May 31, 2023
Published online: June 16, 2023

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Abstract

BACKGROUND

Although esophageal candidiasis (EC) may manifest in immunocompetent individuals, there is a lack of consensus in the current literature about predisposing conditions that increase the risk of infection.

AIM

To determine the prevalence of EC in patients without human immunodeficiency virus (HIV) and identify risk factors for infection.

METHODS

We retrospectively reviewed inpatient and outpatient encounters from 5 regional hospitals within the United States (US) from 2015 to 2020. International Classification of Diseases, Ninth and Tenth Revisions were used to identify patients with endoscopic biopsies of the esophagus and EC. Patients with HIV were excluded. Adults with EC were compared to age, gender, and encounter-matched controls without EC. Patient demographics, symptoms, diagnoses, medications,

and laboratory data were obtained from chart extraction. Differences in medians for continuous variables were compared using the Kruskal-Wallis test and categorical variables using chi-square analyses. Multivariable logistic regression was used to identify independent risk factors for EC, after adjusting for potential confounding factors.

RESULTS

Of the 1969 patients who had endoscopic biopsies of the esophagus performed from 2015 to 2020, 295 patients had the diagnosis of EC. 177 of 1969 patients (8.99%) had pathology confirming the diagnosis of EC and were included in the study for data collection and further analysis. In comparison to controls, patients with EC had significantly higher rates of gastroesophageal reflux disease (40.10% *vs* 27.50%; $P = 0.006$), prior organ transplant (10.70% *vs* 2%; $P < 0.001$), immunosuppressive medication (18.10% *vs* 8.10%; $P = 0.002$), proton pump inhibitor (48% *vs* 30%; $P < 0.001$), corticosteroid (35% *vs* 17%; $P < 0.001$), Tylenol (25.40% *vs* 16.20%; $P = 0.019$), and aspirin use (39% *vs* 27.50%; $P = 0.013$). On multivariable logistic regression analysis, patients with a prior organ transplant had increased odds of EC (OR = 5.81; $P = 0.009$), as did patients taking a proton pump inhibitor (OR = 1.66; $P = 0.03$) or corticosteroids (OR = 2.05; $P = 0.007$). Patients with gastroesophageal reflux disease or medication use, including immunosuppressive medications, Tylenol, and aspirin, did not have a significantly increased odds of EC.

CONCLUSION

Prevalence of EC in non-HIV patients was approximately 9% in the US from 2015-2020. Prior organ transplant, proton pump inhibitors, and corticosteroids were identified as independent risk factors for EC.

Key Words: Candidiasis; Esophagus; Endoscopy; Proton pump inhibitors; Transplants; Glucocorticoids

Core Tip: While esophageal candidiasis (EC) is often associated with human immunodeficiency virus (HIV), the prevalence and clinical risk factors for infection in the non-HIV population are less well established. Our study found the prevalence of EC among patients without HIV in the United States to be higher than anticipated, approximately 9%, over a 5-year period. Independent risk factors for infection were prior organ transplant, proton pump inhibitor, or corticosteroid use. The findings of this study may aide clinicians in establishing an early diagnosis and treatment of EC, thereby preventing the later complications of more severe disease.

Citation: Kimchy AV, Ahmad AI, Tully L, Lester C, Sanghavi K, Jennings JJ. Prevalence and clinical risk factors for esophageal candidiasis in non-human immunodeficiency virus patients: A multicenter retrospective case-control study. *World J Gastrointest Endosc* 2023; 15(6): 480-490
URL: https://www.wjgnet.com/1948-5190/full/v15/i6/480.htm
DOI: https://dx.doi.org/10.4253/wjge.v15.i6.480

INTRODUCTION

Infectious esophagitis is well known to occur in immunocompromised patients particularly those with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS). Candida is the most common pathogen isolated in cases of infectious esophagitis with the predominant species being Candida albicans[1]. Classic symptoms reported in patients with esophageal candidiasis (EC) include odynophagia, dysphagia, and chest discomfort[2]. Upper endoscopy plays a critical role in the evaluation of EC. It allows for direct visualization of the esophageal mucosa and may reveal the patchy white plaques most often described in cases of EC. In addition, brush or tissue biopsies of the esophagus have demonstrated the highest sensitivity and specificity for EC[3]. Cytology or histopathology findings of budding yeasts and pseudohyphae or hyphae with invasion of the epithelium provide confirmation of the diagnosis[1].

Persistent EC may result in severe complications such as esophageal hemorrhage, perforation, or strictures; therefore, early detection and eradication of infection are important to improve patient outcomes[4]. Systemic therapy is recommended for treatment of EC in immunosuppressed individuals as opposed to the topical agents used for oropharyngeal disease. Fluconazole is the standard therapy indicated for EC while other medications including echinocandins and amphotericin are typically

reserved for refractory disease[1]. The treatment of EC in non-HIV patients does not differ for those who are symptomatic; however, guidelines are not well established for treatment of patients without symptoms[1,5].

While EC has most often been associated with HIV, a recent study showed a decreasing prevalence of EC among patients with HIV. This decline was attributed to the rise in the use of highly active antiretroviral therapy. In addition, there was an increase in the prevalence of EC among patients without HIV [4]. Although EC can develop in individuals without HIV, studies investigating clinical risk factors for infection in this patient population have been far less to date[1]. The current literature suggests that the use of corticosteroids may increase the risk of infection; however, there has been a lack of consensus about other risk factors including proton pump inhibitor use (PPI)[2,4,6-10].

It is important to identify patients at risk for EC who may benefit from early diagnosis and treatment with antimicrobial agents and avoid costly, invasive interventions in those without predisposing factors [4]. The aim of this study was to determine the prevalence of EC in patients without HIV and identify common clinical presentations and risk factors for EC in this patient population.

MATERIALS AND METHODS

Study design

This retrospective case-control study received approval from the MedStar Health-Georgetown University Institutional Review Board. We retrospectively reviewed inpatient and outpatient encounters from 5 hospitals located in the District of Columbia and Maryland regions of the United States (US) from January 2015 through December 2020. All hospitals were a part of MedStar Health, a non-profit regional healthcare system. The hospitals included 2 academic tertiary care centers, Georgetown University Hospital and Washington Hospital Center, and 3 community hospitals, Franklin Square Medical Center, Good Samaritan Hospital, and Union Memorial Hospital.

Study population

The International Classification of Diseases, Ninth and Tenth Revisions were used to identify patients who had endoscopic biopsies of the esophagus (ICD-9-CM 42.24 and ICD-10-PCS 0DB58ZX, 0DB18ZX, 0DB28ZX, 0DB38ZX). Patients with a diagnosis of HIV/AIDS (ICD-9-CM 042 or ICD-10-CM B20) were excluded. In addition, vulnerable populations such as minors (age less than 18 years old), pregnant women, and prisoners were excluded. Cases of EC were then identified using the diagnostic codes ICD-9-CM 112.84 and ICD-10-CM B37.8. The diagnosis of EC was confirmed with cytology or histopathology from brush or tissue biopsies of the esophagus. Patients without pathology results confirming the diagnosis of EC were excluded. The control group was formed by patients who had endoscopic biopsies of the esophagus and did not have a diagnosis of EC that were propensity matched in a 1 to 1 ratio to cases of EC using age, gender, and encounter type (inpatient *vs* outpatient).

Data collection

Patient demographics, symptoms, diagnoses, medications, and laboratory data were obtained from the documented outpatient or inpatient encounter preceding the upper endoscopy. The endoscopy, cytology, and histopathology findings were extracted from reports documented in patient charts. Immunosuppressive medications included the use of chemotherapy, immunomodulators, calcineurin inhibitors, or biological therapies. Medications listed in this study consisted of inhaled, oral, or intravenous formulations. Only patients with complete medical history information were included.

Data analysis

The prevalence of EC was defined as the number of patients with a confirmed diagnosis of EC out of all patients who had endoscopic biopsies of the esophagus obtained during the study period. We summarized the distribution of categorical and continuous variables using frequencies and percentages, and medians with interquartile ranges, respectively. We compared differences in medians for continuous variables using the Kruskal-Wallis test. Differences in categorical variables were evaluated using chi-square analyses. Multivariable logistic regression analyses were performed using EC as the outcome variable, which included adjustments for age, gender, race or ethnicity, body mass index (BMI), heavy alcohol use, gastroesophageal reflux disease (GERD), history of organ transplant, and use of medications such as immunosuppressive agents, PPI, corticosteroids, Tylenol, or aspirin. Statistical significance was defined as P value <0.05. The statistical methods of this study were reviewed by Kavya Sanghavi from MedStar Health Research institute.

RESULTS

Of the 1969 patients who had endoscopic biopsies of the esophagus performed from 2015-2020, 295

patients had the diagnosis of EC. There were 118 patients with the diagnosis of EC who were excluded due to a lack of pathology results confirming the diagnosis of EC or insufficient data for review. 177 of 1,969 patients (8.99%) had pathology confirming the diagnosis of EC and were included in the study for data collection and further analysis. The annual incidence of EC in patients who underwent endoscopy with esophageal biopsy ranged from 7.45% to 10.84% with no significant trend observed over the study period (P = 0.58). Patients with EC had a median age of 65 years old and BMI of 24.48 kg/m^2. There were 91 females (51.40%) and 86 males (48.60%), and their racial and ethnic backgrounds were as follows: 74 White (41.80%), 90 Black (50.80%), and 13 others (7.30%), which included Hispanic, Latine, Asian, and not identified patients. Amongst the study population, there were 295 matched controls identified with 48 patients excluded due to insufficient data for review. Of the 247 matched controls included in the study, the median age was 63 years old, and the median BMI was 26.29 kg/m^2. There were 134 females (54.30%) and 113 males (45.70%), and their racial and ethnic backgrounds were as follows: 127 White (51.40%), 109 Black (44.10%), and 11 others (4.50%). Median age, gender, race, and ethnicity did not significantly differ between EC cases and the controls. However, patients with EC were found to have a significantly lower median BMI than the control group (P = 0.003) (Table 1).

The most common clinical symptoms in patients with EC were dysphagia (16.94%), followed by nausea (14.98%), melena (14.66%), and vomiting (13.68%). Chest pain and odynophagia were present in only 3.91% and 3.26% of EC cases, which was comparable to the rate in patients without EC (4.14% and 2.53%). In the controls, the predominant symptoms were vomiting (18.16%), nausea (17.47%), melena (13.33%), and dysphagia (11.95%) (Table 2). There were few patients with EC who were asymptomatic on presentation representing only 3.58% of cases. Endoscopy findings frequently encountered among patients with EC included white/yellow plaques (44.98%) and esophagitis (21.11%). In 2.08% of EC patients, the esophagus was normal on endoscopy. The controls most often had esophagitis (38.51%), or a hiatal hernia (20.11%) found on endoscopy, with only 2.59% having white/yellow plaques (Figure 1).

In comparison to controls, patients with EC had significantly higher rates of GERD (40.10% *vs* 27.50%; P = 0.006), prior organ transplant (10.70% *vs* 2%; P < 0.001), immunosuppressive medication (18.10% *vs* 8.10%; P = 0.002), PPI (48% *vs* 30%; P < 0.001), corticosteroid (35% *vs* 17%; P < 0.001), Tylenol (25.40% *vs* 16.20%; P = 0.019), and aspirin use (39% *vs* 27.50%; P = 0.013). Heavy alcohol use was less frequent in patients with EC than those without EC (9% *vs* 17%; P = 0.19). There was no significant difference in the rates of tobacco use, diabetes, liver cirrhosis, end-stage renal disease, active malignancy, or medication use of tumor necrosis factor inhibitors, histamine type-2 receptor antagonists (H2RAs), non-steroidal anti-inflammatory drugs, and antibiotics between the two groups (Table 1). On multivariable logistic regression analysis, patients with a prior organ transplant had increased odds of EC (OR = 5.81; P = 0.009), as did patients taking a PPI (OR = 1.66; P = 0.03) or corticosteroids (OR = 2.05; P = 0.007). In addition, there was a significant association between patients of other races and ethnicities and EC when Whites were used as the reference group (OR = 2.55; P = 0.041). Patients with GERD or medication use, including immunosuppressive medications, Tylenol, and aspirin, did not have a significantly increased odds of EC (Table 3).

Fluconazole monotherapy was the most common treatment used in patients with EC (77.97%). Other treatments used included nystatin monotherapy (1.69%), echinocandin monotherapy (1.13%), amphotericin monotherapy (0.56%), and fluconazole with nystatin (3.39%), or with echinocandin (2.26%). There were 12.99% of patients with EC who did not receive treatment with anti-fungal therapy. Of the 154 patients with EC who received anti-fungal therapy, 60 had follow-up data available for review. Approximately half of these patients (32/60) experienced symptom resolution after completing the prescribed treatment course.

Additional findings noted in the present study included the presence or absence of oral candidiasis, viral esophagitis, or esophageal carcinoma. Oral candidiasis was present in 5 patients with EC and 2 patients without EC. There was 1 patient with EC who had histopathology demonstrating coinfection with herpes simplex virus. In the controls, 3 patients had histopathology consistent with HSV infection alone. Esophageal squamous cell carcinoma was present on histopathology in 9 patients with EC and 5 patients without EC. There were 6 patients with esophageal adenocarcinoma on histopathology in the controls, while none of the patients with EC had esophageal adenocarcinoma on histopathology.

DISCUSSION

While EC has long afflicted patients with HIV, its presence among the non-HIV population along with the predisposing conditions for infection are less well known. In our study, the overall prevalence of EC in patients without HIV was approximately 9% with annual incidence ranging from 7.5% to 10.8% with no significant trend observed over the study period from 2015-2020. The prevalence/incidence of EC in our study was higher than rates previously reported in the literature, which ranged from 0.32% to 5.2% [4,8,9,11]. Studies with a lower prevalence/incidence of EC tended to be older and conducted in East Asian territories while a more recent study within the US had a higher overall incidence of 5.2%[4,8,9,11]. This may suggest an increasing prevalence of EC among patients without HIV or a greater predominance of EC within the US population. In addition, the prevalence of EC may have been underes-

Table 1 Study population and comparison of patients with and without esophageal candidiasis, *n* (%)

Risk factor	EC[1] patients, *n* = 177	Matched controls, *n* = 247	*P* value
Age (yr)	65.00	63.17	0.637
BMI[1] (kg/m^2)	24.48	26.29	**0.003**
Gender			0.564
Female	91 (51.40)	134 (54.30)	
Male	86 (48.60)	113 (45.70)	
Race and ethnicity			0.104
White	74 (41.80)	127 (51.40)	
Black	90 (50.80)	109 (44.10)	
Other[1]	13 (7.30)	11 (4.50)	
Heavy alcohol use	16 (9.00)	42 (17.00)	**0.019**
Tobacco use	97 (54.80)	123 (49.80)	0.309
GERD[1]	71 (40.10)	68 (27.50)	**0.006**
Diabetes	63 (35.60)	71 (28.70)	0.135
Liver cirrhosis	9 (5.10)	7 (2.80)	0.23
End stage renal disease	24 (13.60)	26 (10.60)	0.347
Transplant recipient	19 (10.70)	5 (2.00)	**< 0.001**
Active Malignancy	32 (18.10)	32 (13.00)	0.146
Immunosuppressive medication use[1]	32 (18.10)	20 (8.10)	**0.002**
TNF inhibitor use[1]	1 (0.60)	1 (0.40)	0.812
Proton pump inhibitor use	85 (48.00)	74 (30.00)	**< 0.001**
H2RA use	21 (11.90)	30 (12.10)	0.93
Corticosteroid use	62 (35.00)	42 (17.00)	**< 0.001**
Tylenol use	45 (25.40)	40 (16.20)	**0.019**
NSAID use[1]	18 (10.20)	21 (8.50)	0.558
Aspirin use	69 (39.00)	68 (27.50)	**0.013**
Bisphosphonate use	3 (1.70)	2 (0.80)	0.405
Antibiotic use	22 (12.40)	19 (7.70)	0.104

[1]Immunosuppressive medication includes chemotherapy, immunomodulator, calcineurin inhibitors, or biological therapies. EC: Esophageal candidiasis; BMI: Body mass index; Race and ethnicity other subcategory, includes Hispanic, Latine, Asian and not identified; GERD: Gastroesophageal reflux disease; TNF: Tumor necrosis alpha; H2RA: Histamine type-2 receptor antagonist; NSAID: Non-steroidal anti-inflammatory.

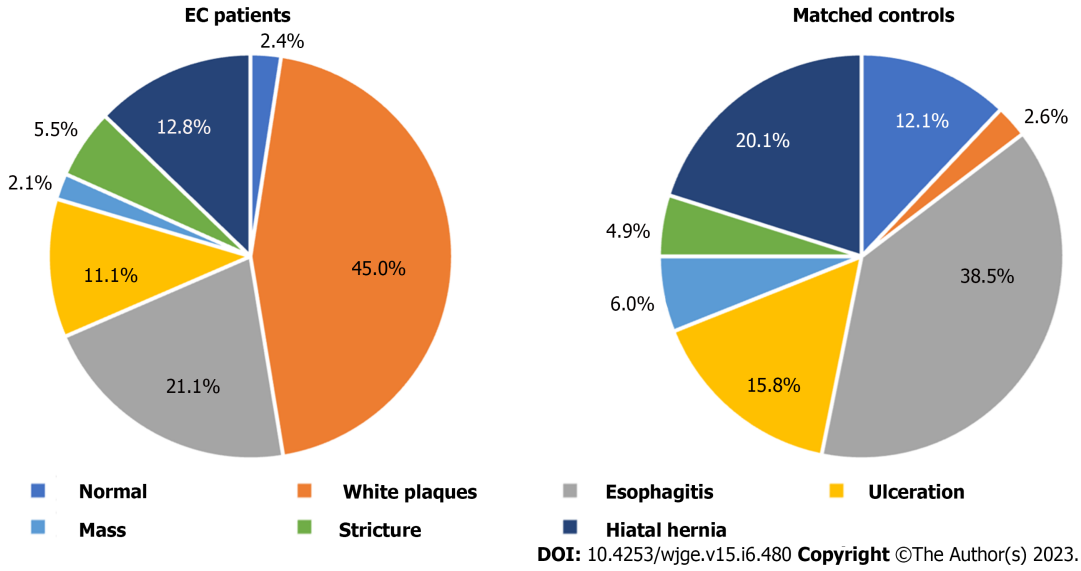
timated in other studies due to methodological limitations such as including only patients undergoing routine health physicals or requiring the presence of white plaques on endoscopy for the diagnosis, which according to our results represents less than half of EC cases[4,8,11].

We found that most patients with EC in our study were elderly with a median age of 65 years old; however, increasing age was not found to be a significant risk factor for EC. Similar ages were reported in other studies ranging from 51 to 65 years. old, but unlike the present study, they demonstrated a significant association between increasing age and EC[4,11,12]. Due to the waning of epithelial cell immunity over time, older age has been thought to increase susceptibility to infections of the esophagus, which may include EC[7]. In our study, BMI was significantly lower in patients with EC (median 24.5) compared to controls (median 26.3), and increasing BMI was not associated with an increased risk of EC. A study by Ogiso *et al*[2] also found that patients with EC were less likely to have a high BMI. Patients with low BMIs are thought to be at an elevated risk for oropharyngeal candidiasis due to immune dysfunction related to malnutrition; however, further studies are needed to evaluate this relationship specifically in cases of EC[2].

Table 2 Comparison of presenting symptoms in patients with and without esophageal candidiasis, *n* (%)

Presenting symptom	EC[1] patients, *n* = 177	Matched controls, *n* = 247
Dysphagia	52 (16.94)	52 (11.95)
Nausea	46 (14.98)	76 (17.47)
Melena	45 (14.66)	58 (13.33)
Vomiting	42 (13.68)	79 (18.16)
Hematemesis	26 (8.47)	44 (10.11)
Epigastric pain	21 (6.84)	22 (5.06)
Weight loss	18 (5.86)	8 (1.84)
Non-specific	17 (5.54)	36 (8.28)
Abdominal pain		
Diarrhea	13 (4.23)	7 (1.61)
Chest pain	12 (3.91)	18 (4.14)
Asymptomatic	11 (3.58)	11 (2.53)
Odynophagia	10 (3.26)	11 (2.53)
Dyspepsia	6 (1.95)	9 (2.07)
Acid reflux	5 (1.63)	2 (0.46)
Unknown	0 (0.00)	2 (0.46)

[1]EC: Esophageal candidiasis; Unknown: presence or absence of symptoms not reported.



DOI: 10.4253/wjge.v15.i6.480

Figure 1 Comparison of upper endoscopy findings in patients with and without esophageal candidiasis. EC: Esophageal candidiasis.

The classic symptoms of infectious esophagitis have been described as dysphagia, odynophagia, and chest pain, although in some cases patients may remain asymptomatic[5]. We found that patients with EC presented most often with dysphagia (16.94%) while odynophagia and chest pain manifested in only a small percentage of patients (3.26% and 3.91%). In addition, there were few cases of EC that were asymptomatic (3.58%). Overall, greater than two thirds of patients with EC presented with non-specific gastrointestinal symptoms other than those typically attributed to infectious esophagitis. Chen *et al*[11] also reported a low number of EC cases that presented with dysphagia and chest pain (2.1% and 14.9%) and none of the patients had odynophagia. Another study found more than half of patients with EC were asymptomatic on presentation while only 11.7% of patients had dysphagia, chest pain, or odynophagia[8]. These findings suggest that EC may be discovered in non-HIV patients who have non-specific upper gastrointestinal symptoms, which may be attributed to EC or another co-existing

Table 3 Multivariate analysis of risk factors for esophageal candidiasis

Risk factor	Odds ratio	*P* value
Gender		
Female	Reference	
Male	1.28	0.269
Race and ethnicity		
White	Reference	
Black	1.50	0.080
Other[1]	2.55	**0.041**
Age	1.00	0.720
BMI[1]	0.99	0.209
Heavy alcohol use	0.51	0.059
GERD[1]	1.60	0.051
Transplant recipient	5.81	**0.009**
Immunosuppressive medication use[1]	0.87	0.746
Proton pump inhibitor use	1.66	**0.030**
Corticosteroid use	2.05	**0.007**
Tylenol use	1.57	0.092
Aspirin use	1.45	0.115

[1]Immunosuppressive medication defined as chemotherapy, immunomodulator, calcineurin inhibitors, or biological therapies. BMI: Body mass index; Race and ethnicity other subcategory, includes Hispanic, Latine, Asian and not identified; GERD: Gastroesophageal reflux disease.

gastrointestinal condition with asymptomatic infection. Mimidis *et al*[12] proposed that there could be a relationship between the presenting symptom of EC and the predisposing factor for infection. The authors found that corticosteroid and acid suppressor use correlated with chest discomfort on presentation. While odynophagia was common in patients with malignancy, dysphagia was more often found in those with motility disorders. Clinicians should remain vigilant for EC in those with risk factors for infection but without the classic symptoms associated with infectious esophagitis as atypical presentations are more common in non-HIV patients.

In patients with HIV, oral candidiasis often occurs concurrently with EC; however, this manifestation has not been fully evaluated in the non-HIV population[7]. It is thought that oral immunity is impaired early in the course of HIV infection due to salivary gland dysfunction allowing for the overgrowth of yeast[4]. One study conducted in a non-HIV patient population reported no cases of oral candidiasis among those diagnosed with EC[6]. In another study by Chocarro Martínez *et al*[13], there were only 3.9% of patients with EC who also had findings of oral candidiasis. In the present study, oral candidiasis was found in 2.8% of EC cases among patients without HIV. The lack of simultaneous oropharyngeal disease in non-HIV patients suggests that impaired oral immunity may not be required for the pathogenesis of EC in this patient population.

The usual endoscopic characteristics reported in cases of EC include creamy white plaques early in the disease course with later progression to friable mucosa with ulcerations and strictures[12]. In the HIV population, increased severity of esophageal infection has been shown to correlate with lower CD4 counts[12]. We found in our non-HIV population that nearly half of patients with EC had white/yellow plaques present on endoscopy. Fewer patients had findings of more severe disease such as esophagitis, ulcerations, or strictures and about 2% had a normal esophagus on endoscopy. In similar studies by Nassar *et al*[7] and Alsomali *et al*[9], most patients with EC had white plaques present on endoscopy with a limited number showing signs of severe infection and approximately 3%-5% had a normal esophagus. These findings indicate that EC may present with milder disease on endoscopic evaluation in non-HIV patients and in some cases without white plaques or with a normal esophagus, thus requiring biopsy for histopathologic diagnosis.

The present study showed that PPI use was a significant risk factor for the development of EC in patients without HIV. This association was not observed in patients with H2RA use, which may be attributed to the greater acid suppression achieved by PPIs. It has been proposed that hypochlorhydria may permit colonization of the stomach by oral cavity yeasts thereby increasing the risk for esophageal infection[12]. While GERD was more common in patients with EC than those without EC, we found that

GERD was not associated with an increased risk of EC. This suggests that the acid suppression from PPIs is likely responsible for the observed association with EC rather than the disease this medication is used to treat. These findings are supported by the results of other studies in the current literature. Chocarro *et al*[13] also demonstrated a significant relationship between omeprazole use and EC, which was not seen with H2RA use. In a large retrospective cohort study, three-quarters of patients with EC were found to be taking a PPI at the time of diagnosis. In addition, there was a subset of 15 patients who had endoscopy confirmed EC following initiation or dose increase of PPI therapy[7]. Although there were two studies in our search of the literature that did not find a significant relationship between PPI use and EC, the present study adds to those that have identified PPIs as an independent risk factor for EC in patients without HIV[4,8].

We found that corticosteroid use significantly increased the risk of EC in patients without HIV. This was consistent with the results of prior studies that also demonstrated an association between corticosteroid use and the development of EC[6,8,11,13]. One large retrospective cohort study found that a higher-prednisone equivalent dose further increased the risk of EC, which they attributed to the greater impairment in cellular immunity achieved with higher doses of steroids[4]. The increased risk of EC with corticosteroid use is likely related to the suppression of immune cell function systemically or within the esophagus with swallowing of inhaled corticosteroids[12]; however, additional studies are needed to elucidate the risk of EC with systemic compared to inhaled formulations.

Fungal infections are known to be a significant cause of morbidity and mortality in solid organ transplant recipients. Candida is the most frequently isolated pathogen in this patient population with the greatest risk of infection early in the post-transplant period. Mucosal infections are common as seen with the increased frequency of oral candidiasis in these patients[14]. The susceptibility to fungal infections observed in transplant recipients has been attributed to the use of high-dose steroids, episodes of rejection, hyperglycemia, leukopenia, and old age[15]. While cases of EC have been reported in the literature, the association between EC and history of prior organ transplant has not been fully elucidated. A retrospective review of renal transplant recipients hospitalized for fungal infections in the US found that Candida was responsible for over 80% of infections with the esophagus being the most frequent site in 31.9% of cases. Of note, HIV status was not reported for the patients included in this study[16]. In our study, history of prior organ transplant was a significant risk factor for the development of EC independent of using corticosteroids or immunosuppressive medications, which included chemotherapeutics, immunomodulators, calcineurin inhibitors, and biologic agents.

Unlike in oropharyngeal disease, EC requires treatment with systemic rather than local antifungal therapy. Fluconazole is considered the first-line therapy for EC with dosages ranging from 200 to 400 mg daily for a total of 2 to 3 wk. Treatment failure has been observed in cases of fluconazole resistance, which is often related to the frequency and duration of prior therapy and the emergence of Candida species with greater azole resistance[5]. Fluconazole was the treatment of choice for most patients with EC in our study as few patients received treatment with other anti-fungal therapies. Interestingly, only about half of patients with EC experienced resolution of symptoms with anti-fungal treatment. Another study also reported fluconazole as the predominant therapy used for treatment of EC. In patients who had a follow-up endoscopy, approximately 24% had persistence of Candida infection and half of these patients had received anti-fungal treatment[8]. Given these findings, the prevailing Candida species and fluconazole resistance rates in patients without HIV may differ from those with HIV and further investigation is needed to guide future treatment recommendations.

Our results were subject to limitations of the retrospective observational study design. EC cases were identified from inpatient and outpatient encounters at hospital facilities, which did not include ambulatory surgery centers, and follow-up data was limited. As patients had various indications for endoscopy, it is unclear whether the presence of candida on histopathology was consistent with a clinically significant infection. A major strength of this study was the patient population, which included both inpatient and outpatient encounters as well as age, gender, and encounter-matched controls. In addition, the data was collected over the more recent years from multiple hospitals with differing levels of care, thus limiting referral bias. Patients with an established diagnosis of HIV were excluded, which has been performed in few studies of EC. We also confirmed that patients with a diagnosis of EC had histopathology demonstrating the presence of Candida.

CONCLUSION

In conclusion, this study determined the prevalence of EC in the non-HIV patient population to be approximately 9% from 2015 through 2020. EC should remain on the differential in patients with risk factors for infection presenting with non-specific gastrointestinal complaints as the classic symptoms of infectious esophagitis are less common in patients without HIV. Clinicians may consider esophageal biopsy in patients with risk factors for EC presenting with typical or atypical symptoms and a normal esophagus on endoscopy for histopathologic diagnosis. However, further studies are needed in patients with a histopathologic diagnosis of EC who are asymptomatic and have normal findings on endoscopy to determine if treatment is required for eradication of infection. Identification of high-risk patients is

critical for the early diagnosis and treatment of EC to prevent later complications with progression to more severe disease. In our retrospective case-control study, prior organ transplant, PPIs, and corticosteroids were identified as independent risk factors for the development of EC in patients without HIV.

ARTICLE HIGHLIGHTS

Research background

Infectious esophagitis is well known to occur in immunocompromised patients particularly those with human immunodeficiency virus with Candida being the most common pathogen isolated.

Research motivation

While esophageal candidiasis (EC) has most often been associated with human immunodeficiency virus (HIV), a recent study showed a decreasing prevalence of EC among patients with HIV and an increase in the prevalence of EC among patients without HIV. Although EC can develop in individuals without HIV, studies investigating clinical risk factors for infection in this patient population have been far less to date. We designed this study to determine the prevalence, clinical manifestations, and risk factors for EC in a non-HIV patient population.

Research objectives

The aim of this study was to determine the prevalence of EC in patients without HIV and identify common clinical presentations and risk factors for EC in this patient population.

Research methods

This retrospective case-control study encompassed inpatient and outpatient encounters from 5 hospitals located in the District of Columbia and Maryland regions of the United States. Cases of EC were identified among patients who had endoscopic biopsies of the esophagus and the presence of EC on cytology and/or histopathology. Patients with HIV were excluded. Multivariable logistic regression was used to identify independent risk factors for EC, after adjusting for potential confounding factors.

Research results

This study determined the prevalence of EC in the non-HIV patient population to be approximately 9% from 2015 through 2020. We found that patients with EC presented most often with non-specific gastrointestinal complaints while odynophagia and chest pain manifested in only a small percentage of patients. Less than half of patients with EC had white/yellow plaques present on endoscopy. Prior organ transplant, proton pump inhibitors, and corticosteroids were identified as independent risk factors for EC.

Research conclusions

The prevalence of EC in our study was higher than expected based upon rates reported in prior studies. Classic symptoms of infectious esophagitis are less common in patients without HIV. Clinicians may consider esophageal biopsy for histopathologic diagnosis in patients with risk factors for EC presenting with atypical symptoms and/or absence of white plaques on endoscopy. Significant risk factors for infection in our study were a history of organ transplant, proton pump inhibitor, or corticosteroids use.

Research perspectives

Further studies are needed to evaluate for an increasing prevalence of EC and risk factors for infection in the non-HIV patient population.

ACKNOWLEDGEMENTS

We would like to acknowledge the biostatistical support provided by the MedStar Health Research Institute.

FOOTNOTES

Author contributions: All authors contributed to the study conception and design; material preparation, data collection, and analysis were performed by all authors listed; the first draft of the manuscript was written by Alexandra V Kimchy and all authors commented on previous versions of the manuscript; all authors read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the MedStar Health-Georgetown University Institutional Review Board.

Informed consent statement: The study was exempt from informed consent based on the MedStar Health-Georgetown University Institutional Review Board.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: Datasets are available from the corresponding author at Alexandra.v.kimchy@medstar.net.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Cai YX

REFERENCES

1 **Hoversten P**, Kamboj AK, Katzka DA. Infections of the esophagus: an update on risk factors, diagnosis, and management. *Dis Esophagus* 2018; **31** [PMID: 30295751 DOI: 10.1093/dote/doy094]
2 **Ogiso H**, Adachi S, Mabuchi M, Horibe Y, Ohno T, Suzuki Y, Yamauchi O, Kojima T, Takada E, Iwama M, Saito K, Iwashita T, Ibuka T, Yasuda I, Shimizu M. Risk factors for the development of esophageal candidiasis among patients in community hospital. *Sci Rep* 2021; **11**: 20663 [PMID: 34667198 DOI: 10.1038/s41598-021-00132-w]
3 **Underwood JA**, Williams JW, Keate RF. Clinical findings and risk factors for Candida esophagitis in outpatients. *Dis Esophagus* 2003; **16**: 66-69 [PMID: 12823199 DOI: 10.1046/j.1442-2050.2003.00305.x]
4 **Takahashi Y**, Nagata N, Shimbo T, Nishijima T, Watanabe K, Aoki T, Sekine K, Okubo H, Sakurai T, Yokoi C, Kobayakawa M, Yazaki H, Teruya K, Gatanaga H, Kikuchi Y, Mine S, Igari T, Takahashi Y, Mimori A, Oka S, Akiyama J, Uemura N. Long-Term Trends in Esophageal Candidiasis Prevalence and Associated Risk Factors with or without HIV Infection: Lessons from an Endoscopic Study of 80,219 Patients. *PLoS One* 2015; **10**: e0133589 [PMID: 26208220 DOI: 10.1371/journal.pone.0133589]
5 **Ahuja NK**, Clarke JO. Evaluation and Management of Infectious Esophagitis in Immunocompromised and Immunocompetent Individuals. *Curr Treat Options Gastroenterol* 2016; **14**: 28-38 [PMID: 26847359 DOI: 10.1007/s11938-016-0082-2]
6 **Yakoob J**, Jafri W, Abid S, Jafri N, Islam M, Hamid S, Shah HA, Hussainy AS. Candida esophagitis: risk factors in non-HIV population in Pakistan. *World J Gastroenterol* 2003; **9**: 2328-2331 [PMID: 14562403 DOI: 10.3748/wjg.v9.i10.2328]
7 **Nassar Y**, Eljabbour T, Lee H, Batool A. Possible Risk Factors for Candida Esophagitis in Immunocompetent Individuals. *Gastroenterology Res* 2018; **11**: 195-199 [PMID: 29915629 DOI: 10.14740/gr1019w]
8 **Choi JH**, Lee CG, Lim YJ, Kang HW, Lim CY, Choi JS. Prevalence and risk factors of esophageal candidiasis in healthy individuals: a single center experience in Korea. *Yonsei Med J* 2013; **54**: 160-165 [PMID: 23225813 DOI: 10.3349/ymj.2013.54.1.160]
9 **Alsomali MI**, Arnold MA, Frankel WL, Graham RP, Hart PA, Lam-Himlin DM, Naini BV, Voltaggio L, Arnold CA. Challenges to "Classic" Esophageal Candidiasis: Looks Are Usually Deceiving. *Am J Clin Pathol* 2017; **147**: 33-42 [PMID: 28158394 DOI: 10.1093/ajcp/aqw210]
10 **Hoversten P**, Otaki F, Katzka DA. Course of Esophageal Candidiasis and Outcomes of Patients at a Single Center. *Clin Gastroenterol Hepatol* 2019; **17**: 200-202.e1 [PMID: 29702297 DOI: 10.1016/j.cgh.2018.04.035]
11 **Chen YH**, Jao TM, Shiue YL, Feng IJ, Hsu PI. Prevalence and risk factors for Candida esophagitis among human immunodeficiency virus-negative individuals. *World J Clin Cases* 2022; **10**: 10896-10905 [PMID: 36338217 DOI: 10.12998/wjcc.v10.i30.10896]
12 **Mimidis K**, Papadopoulos V, Margaritis V, Thomopoulos K, Gatopoulou A, Nikolopoulou V, Kartalis G. Predisposing factors and clinical symptoms in HIV-negative patients with Candida oesophagitis: are they always present? *Int J Clin Pract* 2005; **59**: 210-213 [PMID: 15854199 DOI: 10.1111/j.1742-1241.2004.00249.x]
13 **Chocarro Martínez A**, Galindo Tobal F, Ruiz-Irastorza G, González López A, Alvarez Navia F, Ochoa Sangrador C, Martín Arribas MI. Risk factors for esophageal candidiasis. *Eur J Clin Microbiol Infect Dis* 2000; **19**: 96-100 [PMID: 10746494 DOI: 10.1007/s100960050437]
14 **Silveira FP**, Husain S. Fungal infections in solid organ transplantation. *Med Mycol* 2007; **45**: 305-320 [PMID: 17510855

DOI: 10.1080/13693780701200372]

15 **Karuthu S**, Blumberg EA. Common infections in kidney transplant recipients. *Clin J Am Soc Nephrol* 2012; **7**: 2058-2070 [PMID: 22977217 DOI: 10.2215/CJN.04410512]

16 **Abbott KC**, Hypolite I, Poropatich RK, Hshieh P, Cruess D, Hawkes CA, Agodoa LY, Keller RA. Hospitalizations for fungal infections after renal transplantation in the United States. *Transpl Infect Dis* 2001; **3**: 203-211 [PMID: 11844152 DOI: 10.1034/j.1399-3062.2001.30404.x]

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