

Endoscopic ultrasound-directed transgastric ERCP (EDGE): a retrospective multicenter study

Authors

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ABSTRACT

Background Endoscopic ultrasound-directed transgastric endoscopic retrograde cholangiopancreatography (ERCP; EDGE) is an alternative to enteroscopy- and laparoscopy-assisted ERCP in patients with Roux-en-Y gastric bypass anatomy. Although short-term results are promising, the long-term outcomes are not known. The aims of this study were: (1) to determine the rates of long-term adverse events after EDGE, with a focus on rates of persistent gastrogastic or jejuno gastric fistula; (2) to identify predictors of persistent fistula; (3) to assess the outcomes of endoscopic closure when persistent fistula is encountered.

Methods This was a multicenter retrospective study involving 13 centers between February 2015 and March 2019. Adverse events were defined according to the ASGE lexicon. Persistent fistula was defined as an upper gastrointestinal series or esophagogastroduodenoscopy showing evidence of fistula.

Results 178 patients (mean age 58 years, 79% women) underwent EDGE. Technical success was achieved in 98% of cases (175/178), with a mean procedure time of 92 minutes. Perioperative adverse events occurred in 28 patients (15.7%; mild 10.1%, moderate 3.4%, severe 2.2%). The four severe adverse events were managed laparoscopically. Persistent fistula was diagnosed in 10% of those sent for objective testing (9/90). Following identification of a fistula, 5/9

patients underwent endoscopic closure procedures, which were successful in all cases.

Conclusions The EDGE procedure is associated with high clinical success rates and an acceptable risk profile. Persistent fistulas after lumen-apposing stent removal are uncommon,

but objective testing is recommended to identify their presence. When persistent fistulas are identified, endoscopic treatment is warranted, and should be successful in closing the fistula.

Introduction

Obesity remains a central public health issue, with rising prevalence in the USA and worldwide [1,2]. Roux-en-Y gastric bypass (RYGB) is a common and highly successful surgical treatment for obesity and its associated medical co-morbidities [3–5]. Patients undergoing RYGB have higher rates of gallstone disease [6,7] and may require endoscopic retrograde cholangiopancreatography (ERCP) to manage bile duct stones or other pancreatobiliary issues. However, endoscopic access to the biliary tree after RYGB is challenging. Conventional ERCP methods include balloon-assisted enteroscopy (BAE-ERCP) or laparoscopy-assisted ERCP (LA-ERCP) [8–10]. BAE-ERCP is limited by suboptimal technical success rates that range from 50%–70% [8,9,11]. LA-ERCP is highly efficacious, but may require conversion to open laparotomy in 5%–13% of cases [9,12]. There is no consensus as to the preferred approach to ERCP after RYGB.

Recently, endoscopic ultrasound (EUS)-directed transgastric ERCP (EDGE) has emerged as an option for ERCP after RYGB [10,13–16]. This technique involves the creation of a temporary transgastric fistula by placing a lumen-apposing metal stent (LAMS) that connects either the gastric pouch or the proximal jejunum to the excluded stomach (► Fig. 1). The LAMS creates a stable connection to the excluded stomach, facilitating antegrade ERCP across the new tract. The advantages of EDGE include its high success rate [10,14], the avoidance of surgery,

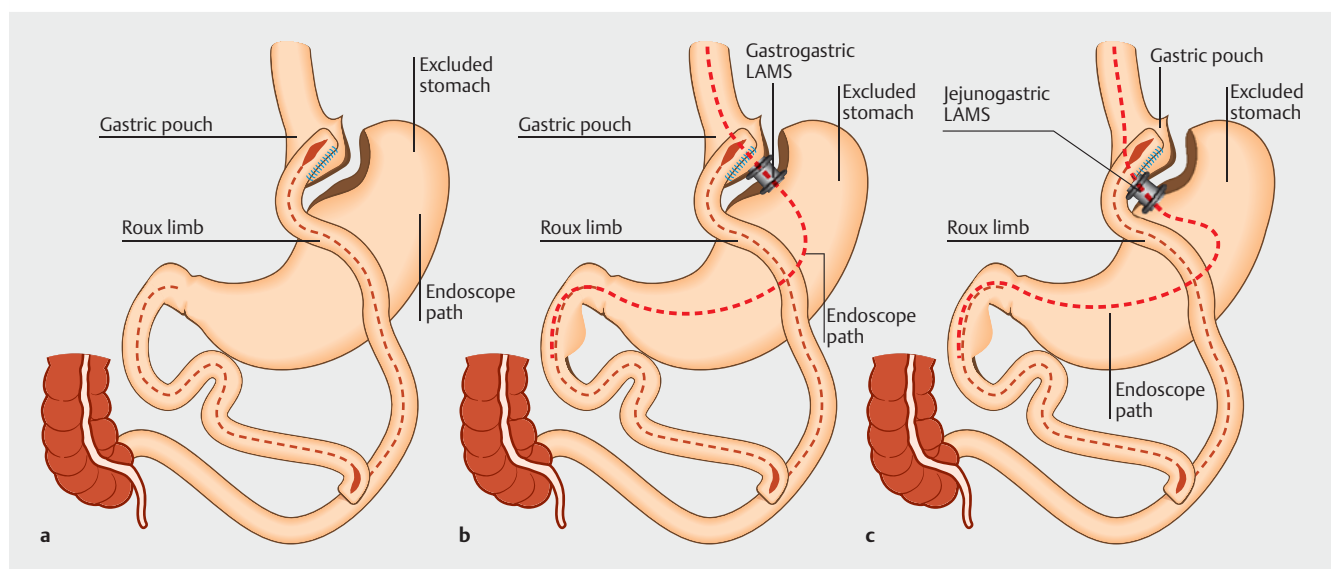
and procedure completion entirely within the endoscopy suite, potentially reducing hospital length of stay (LOS) [17].

The current literature on EDGE is limited. Published studies have included 30 or fewer patients and long-term follow-up data are scant. Specifically, the rates of persistent gastrogastic fistula or jejuno gastric fistula are unknown. The aim of this study was to assess the short-term and long-term outcomes following EDGE, with an emphasis on the rates of persistent gastrogastic and jejuno gastric fistulas.

Methods

We conducted an international, multicenter retrospective cohort study of consecutive patients with a history of RYGB who underwent EDGE at 13 tertiary care centers (12 US centers, 1 European center) between February 2015 and March 2019. Endoscopists at each center had extensive expertise in pancreaticobiliary endoscopy and interventional EUS.

All patients underwent EUS-gastrogastrostomy (EUS-GG) or jejuno gastrostomy (EUS-JG) for ERCP access. Patients undergoing EUS-GG or EUS-JG for indications other than ERCP were excluded. Although 65 patients had been previously reported [10,17–19], those studies were not designed to assess the frequency of or treatment options for persistent fistulas following EDGE. The present study was approved by the Institutional Review Boards and complied with Health Insurance Portability and



► Fig. 1 Diagrams depicting: **a** the upper gastrointestinal tract anatomy following Roux-en-Y gastric bypass; **b,c** the location of the transgastric lumen-apposing metal stent (LAMS) and the path of the endoscope after: **b** gastrogastic stent placement; **c** jejuno gastric stent placement.

Accountability Act (HIPAA) regulations [20] at each participating center.

Procedure techniques

EUS-guided LAMS placement

General anesthesia with endotracheal intubation was used in all patients. A therapeutic linear echoendoscope (GF-UCT180; Olympus, Center Valley, Pennsylvania, USA) was used to identify the excluded stomach from either the gastric pouch or the proximal Roux limb. Doppler imaging was used to avoid intervening vessels. The excluded stomach was punctured with a 19-gauge fine-needle aspiration (FNA) needle. Contrast was injected under fluoroscopic and EUS guidance to confirm correct placement of the needle before further contrast/saline was injected to distend the stomach.

If placement of a non-cautery tip LAMS was planned, wire placement and dilation were performed to facilitate LAMS deployment. In this procedure, a 0.025-inch biliary guidewire (VisiGlide; Olympus) was advanced through the needle and coiled within the stomach. The fistula tract was typically dilated with a 6-mm biliary balloon dilator. Following tract dilation, the LAMS delivery catheter (AXIOS; Boston Scientific, Marlborough, Massachusetts, USA) was advanced over the wire into the excluded stomach, and deployed (**Fig. 1s**, see online-only Supplementary Material). The choice of gastrogastic or jejunogastric puncture was made at the time of the procedure by the endoscopist performing the procedure. When an electrocautery-enhanced LAMS was used, the stent could be deployed either over a guidewire or “freehand,” at the discretion of the endoscopist. Once the excluded stomach had been accessed with the LAMS catheter, the distal flange of the stent was deployed under EUS and fluoroscopic guidance, which was followed by deployment of the proximal flange. The LAMS used had a diameter of 15 or 20 mm.

Initial EDGE was performed either in a single session (LAMS then ERCP on the same day) or in two sessions (LAMS at the first procedure, with ERCP at a later date). For single-session EDGE, the stent lumen was dilated to 15–20 mm with a balloon dilator before ERCP. For two-stage procedures, dilation was performed at the discretion of the endoscopist. Stent fixation techniques (clips, over-the-scope [OTS] clips, or endoscopic suturing) were performed at the discretion of the endoscopists for single-session EDGE (**Fig. 2s**).

Transgastric ERCP and follow-up

Following fistula creation, either a therapeutic duodenoscope (TJF-Q180V; Olympus) or a slim duodenoscope (JF-Q140V, JF-Q160V, or JF-Q180V; Olympus) was advanced across the LAMS into the excluded stomach and ultimately into the second portion of the duodenum for completion of the intended biliary or pancreatic therapies (**Fig. 3s**). If multiple ERCP sessions were required, the gastrogastic or jejunogastric fistula tract was kept open with the transgastric stent. When access was no longer needed, the LAMS was removed with grasping forceps or a snare. If only a single ERCP was needed, LAMS removal was done after 4 weeks (two procedures in total).

After the LAMS had been removed, the fistula tract was managed at the discretion of the performing endoscopist and included no therapy, argon plasma coagulation (APC) applied to the tract, or closure of the fistula edges by endoscopic clip closure, OTS clipping, or endoscopic suturing. Fistula closure after removal of the LAMS was confirmed either by upper gastrointestinal (GI) endoscopy, upper GI series, or cross-sectional imaging, with closure defined as no contrast entry into the excluded stomach, or lack of an endoscopically visible opening.

Study outcomes and definitions

The primary outcome of the study was the technical success of EDGE, defined as successful placement of a transmural LAMS followed by ERCP with cannulation of the intended duct and completion of the intended intervention(s). Secondary outcomes included: short-term adverse events, rates of persistent gastrogastic and jejunogastric fistulas, efficacy and clinical outcomes following endoscopic closure of persistent fistulas, sizes of persistent fistulas, and rates of refractory fistulas. Other procedure-related data, such as procedure time, hospital LOS, and stent dwell time, were also collected.

A persistent fistula was defined as objective evidence (via radiologic study and/or endoscopy) of an ongoing fistula at least 8 weeks after LAMS removal. A refractory fistula was defined as objective evidence of an ongoing fistula that persisted despite endoscopic closure attempt(s). Adverse events were recorded and graded according to the American Society for Gastrointestinal Endoscopy (ASGE) lexicon [21]. Additional clinical information was extracted, including clinical variables known from the surgical literature to affect tissue healing and promote fistula formation, such as diabetes mellitus, coronary artery disease (CAD), and active tobacco use [22, 23].

Statistical analysis

Statistical analysis was performed with Stata software, version 13 (StataCorp, College Station, Texas, USA). Results were reported as mean (standard deviation [SD]), median (interquartile range [IQR]), and percentage for categorical variables. Descriptive statistics were used to summarize the data, and bivariate analyses were performed using the Student's *t* test, chi-squared test, or Fisher's exact test where appropriate. Specifically, Student's *t* test was used to compare the rates of persistent fistula following gastrogastic or jejunogastric LAMS, and in comparisons of mean Charlson comorbidity index (CCI), stent dwell time, and presence of diabetes for cases with/without persistent fistula. Fisher's exact test was used to compare outcomes across centers (**Table 1s**). The threshold for statistical significance (α) was set at a two-sided *P* value of 0.05.

Results

Patient and procedure characteristics

A total of 178 patients who underwent attempted EDGE were identified. The mean age of the patients was 58 (SD 11) years, and 79% were women (**►Table 1**). There were 44 patients (25%) who had diabetes mellitus, while 32 (18%) and 20 (11%) used tobacco and had a history of CAD, respectively. A minority of

► **Table 1** Baseline characteristics of the 178 patients who underwent endoscopic ultrasound-directed transgastric endoscopic retrograde cholangiopancreatography (EDGE).

Demographic data	
▪ Age, mean (SD), years	58 (11)
▪ Sex, female, n (%)	140 (79)
▪ Diabetes, n (%)	44 (25)
▪ Coronary artery disease, n (%)	20 (11)
▪ Tobacco use, n (%)	32 (18)
▪ Cholangitis at time of ERCP, n (%)	15 (8)
▪ Prior failed enteroscopy-assisted ERCP, n (%)	23 (13)
Indication for ERCP, n (%)	
▪ Choledocholithiasis	97 (54)
▪ Bile leak	18 (10)
▪ Benign biliary stricture	16 (9)
▪ Recurrent acute pancreatitis	12 (7)
▪ Malignant biliary stricture	8 (4)
▪ Abnormal imaging study	8 (4)
▪ Pancreatic duct stone	4 (2)
▪ For cholangioscopy NOS	2 (1)
▪ Chronic pancreatitis NOS	1 (1)
▪ Other, n (%)*	12 (7)

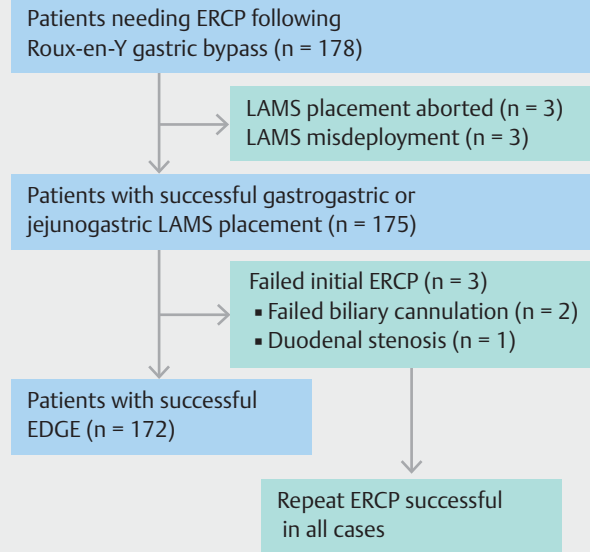
SD, standard deviation; ERCP, endoscopic retrograde cholangiopancreatography; NOS, not otherwise specified.
* Including retained foreign body and sphincter of Oddi (SOD) dysfunction types 1/2.

patients presented with cholangitis (8%) or had failed enteroscopy prior to EDGE (13%).

EUS-guided LAMS placement was successful in 175/178 patients (technical success 98%) (► **Fig. 2**). ERCP was successfully completed in all patients who underwent successful LAMS placement (175/175; 100%) (► **Fig. 2**). Therefore, the technical success of EDGE was 175/178 (98% overall). The number of patients per center is listed in **Table 1s**. There was no significant difference in the technical success of EDGE across centers.

A total of 88 patients (50.2%) underwent EUS-GG, and 87 patients (49.7%) underwent EUS-JG creation. The majority of procedures were performed using a cautery-assisted LAMS (92% [164/178]).

Three patients had failed EUS-LAMS placement. In the first of these, the LAMS misdeployed distally. The gastric perforation was explored and the LAMS was identified entering the excluded stomach. A fully covered esophageal stent was placed across the tract, but ultimately the patient required surgical intervention. In the other two patients, the distal flange was inadvertently drawn back into the gastric pouch. One of these patients had an esophageal stent placed across the transgastric tract and the procedure was aborted without the ERCP being



► **Fig. 2** Flow diagram of the 178 patients who underwent attempted endoscopic ultrasound-directed transgastric endoscopic retrograde cholangiopancreatography (EDGE). Of note, every patient who had successful lumen-apposing metal stent (LAMS) placement ultimately had a successful ERCP, giving an overall technical success rate of EDGE of 98%.

performed. In the other patient, the LAMS was removed and the pouch perforation was closed with an OTS clip. The patient ultimately did not require surgery but, at the time of data collection, definitive therapy for choledocholithiasis had not occurred.

EDGE procedures were completed in a mean time of 92 (SD 47) minutes, with 49% completed in a single session. A 15-mm stent was more commonly used than the newer 20-mm stent (112 [63%] vs. 66 [37%], respectively). The LAMS was secured in 18% of patients (32/178), using an endoscopic suturing system in 29/32 procedures (91%), through-the-scope (TTS) clips in two procedures, and OTS clips in one procedure (► **Table 2**). The median length of hospital stay post-procedure was 0 days (IQR 0–2). The mean follow-up time post-procedure was 5.5 (SD 6) months.

When pancreaticobiliary access was no longer required, the LAMS was removed. At the time of data collection for this study, stent removal had been performed in 153/175 EDGE patients (87%) after a median of 35 days (IQR 22–54). Following LAMS removal, the gastrogastroic or jejunogastric fistula was managed as follows: no treatment in 20% of patients (n=31), and APC alone in 36% of cases (n=55). Endoscopically complete closure of the fistula was performed with endoscopic suturing in 37% (n=57), TTS clips in 5% (n=7) and OTSC in 2% (n=3) (► **Table 3**).

Adverse events

There were a total of 28 early adverse events (15.7%) (► **Table 4**). Across centers, there was no statistically significant difference in the adverse event rates (**Table 1s**). Perforation occurred

► **Table 2** Characteristics of the 178 endoscopic ultrasound-directed transgastric endoscopic retrograde cholangiopancreatography (EDGE) procedures performed.

Gastrogastrostomy, n (%)	88 (50.2) ¹
Jejunogastrostomy, n (%)	87 (49.7) ¹
Performed in a single session, n (%) ²	88 (49)
Procedure time for combined EUS + ERCP, mean (SD), minutes	92 (47)
15-mm LAMS, n (%)	112 (63)
20-mm LAMS, n (%)	66 (37)
Cold LAMS, n (%)	14 (8)
Hot LAMS, n (%)	164 (92)
Stent anchored with suture placement, n (%)	29 (16)
Overall technical success, n (%)	175 (98)

EUS, endoscopic ultrasound; ERCP, endoscopic retrograde cholangiopancreatography; SD, standard deviation; LAMS, lumen-apposing metal stent.

¹ Percentages calculated based on the 175 procedures with successful LAMS placement, rather than 178.

² Note: EDGE performed in a "single session" refers to the initial EDGE procedure only, not subsequent procedures.

► **Table 3** Closure techniques and method of testing for a fistula in the 153 patients who underwent lumen-apposing metal stent (LAMS) removal.*

LAMS dwell time, median (IQR), days	35 (22–54)
Endoscopic closure techniques at LAMS removal, n (%)	
▪ No treatment	31 (20)
▪ APC alone	55 (36)
▪ Endoscopic suturing	57 (37)
▪ Through-the-scope clip	7 (5)
▪ Over-the-scope clip	3 (2)
Fistula testing, n (%)	
▪ Underwent EGD or UGI series to detect fistula	90 (59)
▪ Diagnostic studies positive for persistent fistula	9 (10)

IQR, interquartile range; APC, argon plasma coagulation; EGD, esophago-gastroduodenoscopy; UGI, upper gastrointestinal.

* 22 patients had not undergone endoscopic LAMS removal at time of time of final data collection: LAMS remaining in situ in 19 patients (11%); LAMS migrated spontaneously in 3 patients (2%).

in six patients (3%), five of which occurred during EUS-guided transgastric (n = 1) or transjejunal (n = 4) stent placement, and there was one sphincterotomy-associated perforation that occurred during ERCP. Five perforations were managed with endoscopic closure (n = 4) or conservative measures, including nasogastric tube placement, bowel rest, and intravenous antibiotics (n = 1); one patient required surgery to treat a perforation. Symptomatic capnoperitoneum occurred in three patients (1.5%), requiring laparoscopic decompression in two patients

and percutaneous needle decompression in one. In both cases where surgical decompression was performed, the consulting surgical team performed diagnostic laparoscopy to assess for perforation or leak. When none was found, the abdomen was decompressed via laparoscopy.

Intraprocedural LAMS migration occurred in two patients (1.1%). In both of these patients, EDGE was aborted and not re-attempted; these patients are included in the three failed EUS cases. Misdeployment of the LAMS requiring management prior to EDGE completion occurred in nine patients (5%). In all cases this was managed with placement of a bridging esophageal stent or a second LAMS, allowing completion of the procedures.

Other adverse events included: procedure-related bleeding requiring transfusion in two patients (1.1%), delayed stent migration in two patients (1.1%), post-ERCP pancreatitis in three patients (1.7%), and cholangitis due to ERCP in one patient (0.6%). Adverse events were rated severe in four patients (2.2%), moderate in six (3.4%), and mild in 18 (10.1%).

Persistent fistula

Characteristics and predictive factors

A total of 90 patients (59% of those who underwent LAMS removal) were tested for persistent fistula following LAMS placement. Nine patients (10% of those tested) were found to have a persistent fistula at least 8 weeks after LAMS removal. The clinical characteristics and outcomes of the patients with persistent fistulas are summarized in **Table 2s**.

There was no statistically significant difference between the rate of persistent fistula following placement of a gastrogastrostomy LAMS (9% [4/45 patients]) vs. jejunogastric LAMS (11% [5/45]; $P = 0.73$). On bivariate analysis, there were trends toward longer median stent dwell time for persistent fistula (50 days vs. 34 days; $P = 0.09$) and higher mean CCI score (2.6 [SD 1.5] vs. 1.5 [SD 1.8]; $P = 0.10$), but these differences did not reach statistical significance. None of the nine patients with persistent fistula underwent any attempted fistula closure at LAMS removal (APC alone or no therapy was performed in all of these patients).

On bivariate analysis, diabetes mellitus was significantly more common in those who developed persistent fistula than in those who did not (56% vs. 21%; $P = 0.02$).

Weight changes, endoscopic closure, and clinical outcomes

Nine patients were found to have a persistent fistula following EDGE. One patient declined any further intervention and one underwent surgery for severe chronic pancreatitis, and the excluded stomach was resected at that time. In two cases, the patients had not yet returned for follow-up at the time of data collection (**Table 2s**). Five patients underwent endoscopic therapy for persistent fistula, which was successful in all cases after one (n = 3) or two (n = 2) endoscopic procedures. All five patients had confirmation of fistula closure by objective testing. There were no adverse events associated with endoscopic fistula closure in any patient who underwent these procedures.

Weight changes for patients with a persistent fistula were heterogeneous. Most (6/9 [67%]) had weight loss during the study period, with three patients gaining weight during the study.

► **Table 4** Adverse events following endoscopic ultrasound-directed transgastric endoscopic retrograde cholangiopancreatography (EDGE).

Adverse event	n	Severity*	Management
Perforation	6	Severe (1)	Laparoscopic surgical closure (1)
		Moderate (2)	Closed endoscopically (1) Conservative management (1)
		Mild (3)	Closed endoscopically (3)
Symptomatic pneumoperitoneum	3	Severe (2)	Laparoscopic decompression (2)
		Mild (1)	Needle decompression, no further intervention (1)
LAMS migration, intraprocedural	2	Severe (1)	Hypotension, intubation, ICU stay (1)
		Mild (1)	Procedure aborted (1)
LAMS misdeployment requiring bridging stent	9	Moderate (1)	Bridging stent placed and procedure completed (9)
		Mild (8)	
LAMS migration, delayed	2	Mild (2)	No intervention required (2)
Bleeding requiring red cell transfusion	2	Moderate (2)	Transfusions of 2 units and 3 units; EGD performed, with no active bleeding in either case (2)
Post-ERCP pancreatitis	3	Mild (3)	Conservative management (3)
Cholangitis	1	Moderate (1)	Intravenous then oral antibiotics (1)

LAMS, lumen-apposing metal stent; ICU, intensive care unit; EGD, esophagogastroduodenoscopy; ERCP, endoscopic retrograde cholangiopancreatography.
* According to ASGE Lexicon [21].

Discussion

Endoscopists face a formidable challenge when managing pancreaticobiliary disease in RYGB patients. Currently, there is no accepted first-line modality to be performed in patients who have undergone prior gastric bypass.

Some centers have embraced the highly efficacious LA-ERCP as a first-line approach, with efficacy rates near 100% in several published studies [12, 24–26]. However, LA-ERCP has multiple downsides including complicated logistics, operating room costs, and laparoscopy-associated adverse events, including the possible need for open surgery [9, 12, 26]. LA-ERCP is not ideal if there is a need for additional ERCPs. In the largest published cohort to date, Abbas et al. found that >15% of patients were left with a percutaneous endoscopic gastrostomy (PEG) tube in place owing to the need for a repeat procedure [12]; other studies have reported the need for a PEG for future access in up to 44% of patients [24]. With a majority of adverse events associated with LA-ERCP arising from the laparoscopy, the potential need for repeat access [12, 24, 25], and with patients increasingly seeking minimally invasive and endoscopic therapies [27, 28], the need for an effective endoscopic approach to ERCP following RYGB is clear.

Single-balloon or double-balloon enteroscopy have historically been the initial technique offered. Advantages include the avoidance of surgical intervention and lower costs compared with LA-ERCP [8, 9]. However, success rates range from 60% to 88% [8–10, 29–31], compared with efficacy rates of 98%–100% in the published literature on LA-ERCP [8, 9, 12, 25, 29]. Even with relatively low complication rates, low rates of successful BAE-ERCP make this procedure difficult to justify.

EDGE, first described 5 years ago [32], bridges the gap between balloon-assisted endoscopic procedures and the more invasive LA-ERCP (► Fig. 1). In this large multicenter study, we found that EDGE was successful in 98% of cases, comparable to rates of 97%–100% in the existing literature [10, 16, 17, 19]. There were 28 early adverse events that occurred following EDGE (15.7% of all cases), with 22 events attributable to the EUS access and six attributable to the ERCP. Events attributable to ERCP (n=6) were mild (n=3) or moderate (n=3) in severity, according to the ASGE lexicon. Events attributable to EUS (n=22) were predominantly mild (n=15) or moderate (n=3) in severity, although there were four severe events, three of which involved laparoscopic intervention and one of which involved a prolonged hospital stay following the procedure. These rates are comparable with those found in the existing literature.

This study focused on the frequency and management of post-EDGE fistulas, given the extremely sparse data on this topic [10, 17, 19]. We report 90 patients who underwent objective testing for fistula. Persistent fistula was found in nine patients (10% of those tested), consisting of five jejuno gastric fistulas and four gastrogastic fistulas. Not all patients returned for further management of the fistula but, in those who did return, endoscopic closure was successful in all cases.

There is concern regarding the creation of an iatrogenic gastrogastic or jejuno gastric fistula for the purposes of performing transgastric ERCP [26, 33–35]. Most worrisome is the theoretical concern that an iatrogenic fistula becomes a chronic fistula that causes weight regain, or precipitates GI symptoms and/or marginal ulcers, with either scenario potentially requiring revisional surgery. However, two pieces of evidence from this study suggest these concerns may be unfounded. First is

the age of the fistula. The published literature on patients needing gastrogastroic fistula repair describes fistulas present for years (mean 1.4–4.8 years post-RYGB) [36–38], compared with fistulas in the EDGE subpopulation, which were present for a mean duration of 49 days (1.6 months). Second, the high success of endoscopic closure in this study suggests post-EDGE fistulas are a distinct clinical entity that are more easily managed. In published studies, the clinical success of gastrogastroic fistula closure is low, ranging from 0%–35% [37, 39]. The success of fistula closure in this study argues that wound healing and tissue integrity are not deranged to the same level as is seen in chronic spontaneous fistulas.

The efficacy of EDGE argues that it should be in the discussion as a first-line modality for ERCP in RYGB patients. However, it is important to recognize the strengths and scope of practice of those at each institution who will take care of these patients. In this study, EDGE procedures were performed by endoscopists with expertise in interventional EUS who were comfortable with the placement and management of LAMSs. There are not standardized criteria for assessing “experience” in interventional EUS or LAMS placement, although these tools may be developed in the future. The continued proliferation of LAMSs, especially the newer large-diameter 20-mm stents, could lead to increasing comfort in performing EDGE. These wider stents theoretically would reduce the chance of stent migration during advancement of the duodenoscope. In addition, both OTS clips and endoscopic suturing devices are much more readily available in endoscopy centers, as are those with experience in their use. These devices can be used to fix the LAMS in position to avoid stent migration during ERCP, although duodenoscope advancement must still be performed carefully [40].

One possible barrier to more widespread use of EDGE is the high cost of the LAMS for the procedure. However, it is not only device costs that should be considered with a procedure such as this. Endoscopic options for ERCP in RYGB typically are associated with minimal post-procedural recovery and the absence of post-ERCP pancreatitis. EDGE can be performed entirely on an outpatient basis. In this study, >50% of patients were discharged following the procedure, accruing zero days in the hospital. Mean hospital LOS was 1.6 days (SD 3). These figures compare favorably with LA-ERCP, for which published LOS varies (1.9–3.9 days) [12, 17, 24, 25]. In a recent analysis, EDGE was found to be more cost-effective than either LA-ERCP or BAE-ERCP [41], including the cost of the devices used. This advantage of EDGE over either of the other two procedures persisted in >90% of modeling simulations in the study. What is needed next is clearly a prospective comparative trial that can compare the efficacy and cost outcomes for EDGE, LA-ERCP, and BAE-ERCP.

There are several limitations to this study. This was a retrospective study with inherent limitations due to its design. Because of the lack of a standard testing protocol, we have objective follow-up testing for fistulas in only about half of patients who underwent EDGE. Some patients who developed a persistent fistula were likely missed among those who were not tested. However, the figures presented here provide the best estimates thus far of the true prevalence of persistent fistula post-

EDGE and will inform sample size calculations for a future prospective study. Another possible limitation of this study is its generalizability. Because procedures in this study were performed by those with specialized expertise in interventional endoscopy, it may be difficult to extrapolate these results to community settings.

In conclusion, EDGE is associated with high clinical success rates and an acceptable risk profile. Persistent fistulas are uncommon, but are detectable 10% of the time after EDGE. Weight trends following EDGE are not a reliable indicator of an underlying fistula. If a persistent fistula occurs after EDGE, our data suggest that this can be readily treated endoscopically, with an excellent clinical outcome. Greater experience in fistula identification and closure in the future will be necessary to draw further conclusions about closure methods at LAMS removal.

Competing interests

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References

- [1] Seidell JC, Halberstadt J. The global burden of obesity and the challenges of prevention. *Ann Nutr Metab* 2015; 66: (Suppl. 02): 7–12
- [2] Hales CM, Fryar CD, Carroll MD et al. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007–2008 to 2015–2016. *JAMA* 2018; 319: 1723–1725
- [3] Fisher BL, Schauer P. Medical and surgical options in the treatment of severe obesity. *Am J Surg* 2002; 184: 59–516

- [4] Schauer PR, Bhatt DL, Kirwan JP et al. Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes. *NEJM* 2017; 376: 641–651
- [5] Buchwald H, Estok R, Fahrback K et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med* 2009; 122: 248–256. e5
- [6] Simonen M, Dali-Youcef N, Kaminska D et al. Conjugated bile acids associate with altered rates of glucose and lipid oxidation after Roux-en-Y gastric bypass. *Obes Surg* 2012; 22: 1473–1480
- [7] Amstutz S, Michel J-M, Kopp S et al. Potential benefits of prophylactic cholecystectomy in patients undergoing bariatric bypass surgery. *Obes Surg* 2015; 25: 2054–2060
- [8] Shah RJ, Smolkin M, Yen R et al. A multicenter, US experience of single-balloon, double-balloon, and rotational overtube-assisted enteroscopy ERCP in patients with surgically altered pancreaticobiliary anatomy (with video). *Gastrointest Endosc* 2013; 77: 593–600
- [9] Schreiner MA, Chang L, Gluck M et al. Laparoscopy-assisted versus balloon enteroscopy-assisted ERCP in bariatric post-Roux-en-Y gastric bypass patients. *Gastrointest Endosc* 2012; 75: 748–756
- [10] Bukhari M, Kowalski T, Nieto J et al. An international, multicenter, comparative trial of EUS-guided gastrogastrostomy-assisted ERCP versus enteroscopy-assisted ERCP in patients with Roux-en-Y gastric bypass anatomy. *Gastrointest Endosc* 2018; 88: 486–494
- [11] Skinner M, Popa D, Neumann H et al. ERCP with the overtube-assisted enteroscopy technique: a systematic review. *Endoscopy* 2014; 46: 560–572
- [12] Abbas AM, Strong AT, Diehl DL et al. Multicenter evaluation of the clinical utility of laparoscopy-assisted ERCP in patients with Roux-en-Y gastric bypass. *Gastrointest Endosc* 2018; 87: 1031–1039
- [13] Kedia P, Tyberg A, Kumta NA et al. EUS-directed transgastric ERCP for Roux-en-Y gastric bypass anatomy: a minimally invasive approach. *Gastrointest Endosc* 2015; 82: 560–565
- [14] Tyberg A, Nieto J, Salgado S et al. Endoscopic ultrasound (EUS)-directed transgastric endoscopic retrograde cholangiopancreatography or EUS: mid-term analysis of an emerging procedure. *Clin Endosc* 2017; 50: 185
- [15] Xu M-M, Carames C, Novikov A et al. One-step endoscopic ultrasound-directed gastro-gastrostomy ERCP for treatment of bile leak. *Endoscopy* 2017; 49: 715–716
- [16] Kedia P, Kumta NA, Widmer J et al. Endoscopic ultrasound-directed transgastric ERCP (EDGE) for Roux-en-Y anatomy: a novel technique. *Endoscopy* 2015; 47: 159–163
- [17] Kedia P, Tarnasky PR, Nieto J et al. EUS-directed transgastric ERCP (EDGE) versus laparoscopy-assisted ERCP (LA-ERCP) for Roux-en-Y gastric bypass (RYGB) anatomy. *J Clin Gastroenterol* 2019; 53: 304–308
- [18] Chiang AL, Gaidhane M, Loren DE et al. 338 Impact of EUS-directed transgastric ERCP (EDGE procedure) access route on technical success and adverse events: a multi-center experience. *Gastrointest Endosc* 2018; 87: AB70–AB71
- [19] James TW, Baron TH. Endoscopic ultrasound-directed transgastric ERCP (EDGE): a single-center US experience with follow-up data on fistula closure. *Obes Surg* 2019; 29: 451–456
- [20] Califf RM, Muhlbaier LH. Health Insurance Portability and Accountability Act (HIPAA) must there be a trade-off between privacy and quality of health care, or can we advance both? *Circulation* 2003; 108: 915–918
- [21] Cotton PB, Eisen GM, Aabakken L et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. *Gastrointest Endosc* 2010; 71: 446–454
- [22] Fernandez Ajr, DeMaria E, Tichansky D et al. Experience with over 3,000 open and laparoscopic bariatric procedures: multivariate analysis of factors related to leak and resultant mortality. *Surg Endosc* 2004; 18: 193–197
- [23] McDermott F, Heeney A, Kelly M et al. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. *Br J Surg* 2015; 102: 462–479
- [24] Grimes KL, Maciel VH, Mata W et al. Complications of laparoscopic transgastric ERCP in patients with Roux-en-Y gastric bypass. *Surg Endosc* 2015; 29: 1753–1759
- [25] May D, Vogels E, Parker D et al. Overall outcomes of laparoscopic-assisted ERCP after Roux-en-Y gastric bypass and sphincter of Oddi dysfunction subgroup analysis. *Endosc Int Open* 2019; 7: E1276–E1280
- [26] Yang D, Draganov PV. ERCP in patients with Roux-en-Y gastric bypass: one size does not fit all. *Gastrointest Endosc* 2019; 89: 646
- [27] Varadarajulu S, Tamhane A, Drelichman ER. Patient perception of natural orifice transluminal endoscopic surgery as a technique for cholecystectomy. *Gastrointest Endosc* 2008; 67: 854–860
- [28] Nam K, Kim DU, Lee TH et al. Patient perception and preference of EUS-guided drainage over percutaneous drainage when endoscopic transpapillary biliary drainage fails: An international multicenter survey. *Endosc Ultrasound* 2018; 7: 48
- [29] Desai SV, Naveed M, Jazwinski A et al. 299 Spiral enteroscopy versus laparoscopic-assisted endoscopy for completion of ERCP in patients with Roux-en-Y gastric bypass surgery. *Gastrointest Endosc* 2011; 73: AB122
- [30] Uchida D, Tsutsumi K, Kato H et al. Potential factors affecting results of short-type double-balloon endoscope-assisted endoscopic retrograde cholangiopancreatography. *Dig Dis Sci* 2020; 65: 1460–1470
- [31] Kashani A, Abboud G, Lo SK et al. Double balloon enteroscopy-assisted endoscopic retrograde cholangiopancreatography in Roux-en-Y gastric bypass anatomy: expert vs. novice experience. *Endosc Int Open* 2018; 6: E885–E891
- [32] Kedia P, Shariha RZ, Kumta NA et al. Internal EUS-directed transgastric ERCP (EDGE): game over. *Gastroenterology* 2014; 147: 566–568
- [33] Dayyeh BKA, Thompson CC, Gostout C. Endoscopic retrograde cholangiopancreatography after Roux-en-Y gastric bypass: challenges and cautions. *Gastroenterology* 2015; 148: 858–859
- [34] Park SW. Commentary on “Endoscopic ultrasound (EUS)-directed transgastric endoscopic retrograde cholangiopancreatography or EUS”. *Clin Endosc* 2017; 50: 102
- [35] Crismale JF, Riff BP, Schwartz M et al. Closure of an iatrogenic gastrogastric fistula created during EUS-directed transgastric ERCP. *VideoGIE* 2016; 1: 61
- [36] Chahine E, Kassir R, Dirani M et al. Surgical management of gastrogastric fistula after Roux-en-Y gastric bypass: 10-year experience. *Obes Surg* 2018; 28: 939–944
- [37] Fernandez-Esparrach G, Lautz DB, Thompson CC. Endoscopic repair of gastrogastric fistula after Roux-en-Y gastric bypass: a less-invasive approach. *Surg Obes Relat Dis* 2010; 6: 282–288
- [38] Ribeiro-Parenti L, De Courville G, Daikha A et al. Classification, surgical management and outcomes of patients with gastrogastric fistula after Roux-En-Y gastric bypass. *Surg Obes Relat Dis* 2017; 13: 243–248
- [39] Mukewar S, Kumar N, Catalano M et al. Safety and efficacy of fistula closure by endoscopic suturing: a multi-center study. *Endoscopy* 2016; 48: 1023–1028
- [40] Irani S, Yang J, Khashab MA. Mitigating lumen-apposing metal stent dislodgment and allowing safe, single-stage EUS-directed transgastric ERCP. *VideoGIE* 2018; 3: 322
- [41] James HJ, James TW, Wheeler SB et al. Cost-effectiveness of endoscopic ultrasound-directed transgastric ERCP compared with device-assisted and laparoscopic-assisted ERCP in patients with Roux-en-Y anatomy. *Endoscopy* 2019; 51: 1051–1058