Digestive and Liver Disease xxx (xxxx) xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Meta-Analysis

Endoscopic ultrasound-guided gastro-enteric anastomosis: A systematic review and meta-analysis

Giulio Antonelli[a,b,e,*], Bojan Kovacevic[b], John Gasdal Karsensten[c], Evangelos Kalaitzakis[b,d], Giuseppe Vanella[a,f], Cesare Hassan[e], Peter Vilmann[b]

[a] Endoscopy Unit, Sant'Andrea University Hospital, "Sapienza" University of Rome, Italy
[b] Gastro Unit, Division of Endoscopy, Copenhagen University Hospital Herlev, Denmark
[c] Gastro Unit, Copenhagen University Hospital Hvidovre, Denmark
[d] Department of Gastroenterology, University Hospital of Heraklion, University of Crete, Heraklion, Greece
[e] Endoscopy Unit, Nuovo Regina Margherita Hospital, Rome, Italy
[f] Pancreatobiliary Endoscopy and EUS division, Pancreas Translational and Clinical Research Center, IRCSS San Raffaele Scientific Institute, Milan, Italy

ARTICLE INFO

Article history:
Received 4 January 2020
Accepted 17 April 2020
Available online xxx

Keywords:
Endoscopic ultrasound
Enteric anastomosis
Gastric outlet obsturction
Lumen apposing metal stent
EDGE

ABSTRACT

Background and aims: Endoscopic ultrasound-guided gastro-enteric anastomosis (EUS-GEA) using lumen-apposing metal stents (LAMS) is emerging as a minimally invasive alternative to surgery across several indications. Literature on this subject is heterogeneous, with variable reporting of techniques and outcomes.

Our aim was to perform a meta-analysis of published data on EUS-GEA, providing a pooled estimate of technical and clinical outcomes.

Methods: The protocol was registered in PROSPERO (Reg. no. CRD42018111110). PubMed, Embase, Scopus, and Web of Science databases were searched until February 2019 for studies describing patients undergoing EUS guided enteric anastomosis. PRISMA methodology was used. Pooled technical and clinical success rates as well as pooled adverse events rates were calculated. Study quality, publication bias, and heterogeneity were explored.

Results: Twelve studies including 290 patients were included, published between 2016 and 2019. All studies but one were retrospective. Main procedure indication was gastric outlet obstruction (62.4%), followed by ERCP access (27.9%) in patients with gastric bypass surgery. Direct puncture technique was the most frequently adopted (68.2%). Pooled technical success rate (12 studies, 290 patients) was 93.5% [95% confidence interval (CI) 89.7–6.0%; I^2:0%], while clinical success rate (11 studies, 260 patients) was 90.1% [95%CI 85.5–93.4%; I^2:0%]. Pooled total adverse events rate (11 cohorts, 261 patients) was 11.7% [95%CI 8.2–16.6%; I^2:0%], mainly mild/moderate: 10.6% [95%CI 7 – 15.6%].

No publication bias or significant heterogeneity was found.

Conclusions: EUS-GEA has a high rate of technical and clinical success when performed in expert centers. The procedure appears to be relatively safe, and might represent a non-inferior minimally invasive alternative to surgery. The paucity of long-term clinical outcomes suggests prudency and need for further research, especially regarding non-malignant indications.

Introduction

Endoscopic ultrasound-guided gastro-enteric anastomosis (EUS-GEA) using lumen-apposing metal stents (LAMS) is emerging as a minimally invasive alternative to surgery for the treatment of many conditions [1]. The first description of the technique on a porcine model was published by Binmoeller and colleagues in 2012 [2], and the first human studies concentrated on patients with gastric outlet obstruction (GOO) [3], both malignant and benign, treated with the positioning of LAMS and connection of the gastric lumen to a duodenal or jejunal segment distal to the obstruction [4]. Furthermore, patients with surgically altered anatomy (bariatric or cancer patients) can now undergo per-oral Endoscopic Retrograde Cholangiopancreatography (ERCP) after the deployment of a gastro-gastric or jejuno-gastric LAMS (EDGE or Endoscopic ultrasound-directed transgastric ERCP) [5], and the indications are further expanding [6].

* Corresponding author at: Endoscopy Unit, Sant 'Andrea University Hospital, "Sapienza" University of Rome, Via di Grottarossa 1035-1039, 00189 Rome, Italy.
E-mail address: giulio.antonelli@gmail.com (G. Antonelli).

https://doi.org/10.1016/j.dld.2020.04.021
1590-8658/

Please cite this article as: G. Antonelli, B. Kovacevic and J.G. Karsensten et al., Endoscopic ultrasound-guided gastro-enteric anastomosis: A systematic review and meta-analysis, Digestive and Liver Disease, https://doi.org/10.1016/j.dld.2020.04.021

Two main techniques (direct access and balloon assisted) have been developed and described, with apparently similar success rates. Single-balloon assisted technique involves the use of a dilating balloon advanced over a guidewire across the stenotic segment under radiological guidance. The balloon is then inflated with fluid and subsequently punctured with a 19 G needle, followed by deployment of LAMS [7]. This technique has been further developed using a special double-balloon catheter, that after inflation creates a closed-off jejunal segment that can be flooded with fluid and easily identified and accessed through the gastric wall [8]. Direct access puncture involves EUS-guided identification and puncture of jejunal loop or gastric pouch, followed by direct deployment of LAMS and subsequent endoscopic and/or fluoroscopic confirmation of correct positioning [9].

EUS-GEA has been shown to be minimally invasive, with a shorter procedure time compared to surgery, at potentially greatly reduced costs, but widespread employment beyond selected highly specialised referral centres is still lacking, probably due to limited published literature on this subject, featuring mainly small case series, and to the various techniques that make it difficult to standardise the procedure and extrapolate results.

Our aim was to perform a meta-analysis of currently available published data on EUS-GEA, providing a pooled estimate of technical and clinical outcomes, as well as adverse events.

Patients and methods

Registration

This review is registered on PROSPERO international database (from University of York Centre for Reviews and dissemination—www.crd.york.ac.uk/prospero/) under number CRD42018111110.

Search strategy and study selection

A search of PubMed/MEDLINE, ISI/Web of Science, Embase, and Scopus databases was performed to identify publications from inception to February 2019, that included patients undergoing EUS-guided placement of LAMS between gastric and/or intestinal lumens, for any indications, and were clinically and/or endoscopically followed up to assess procedure technical and clinical success, as well as peri- and post-procedural adverse events.

Details of the search strategy are presented in *Supplementary Statement 1*.

Titles of all the identified articles were independently screened by two authors (GA and BK) to exclude studies not related to the study topic or meeting one of the exclusion criteria. The remaining potentially relevant studies were screened for eligibility by analysis of the abstract and the full text. All disagreements between the two authors were submitted to a third author (CH) and discussed until consensus was achieved. Studies reporting the proportion of patients undergoing the procedure, and proportions of technical and/or clinical success and adverse events were included in the quantitative synthesis through meta-analysis (see below for inclusion criteria).

An analysis of references of each included article was made in order to retrieve additional eligible studies.

The methodology was developed from the PRISMA [10] checklist.

Inclusion criteria

The analysis included all studies describing a cohort of patients undergoing EUS-GEA, for any indication, clearly reporting at least one of the following outcomes: technical success, clinical success, adverse events (see definitions below).

Exclusion criteria

No study design was rejected *a priori*. Excluded from the analysis were: any studies in a language other than English; case reports or case series with five or fewer patients; reviews; editorials. In the event of centre or patient overlap between series, the respective study corresponding authors were contacted for clarification and further information. When further clarification was not possible, the largest or most recent study was included. Excluded studies and reasons for exclusion were recorded.

Definitions

Technical success was defined uniformly across studies, as the adequate positioning of a LAMS across a gastro-gastrostomy, gastro-enterostomy or entero-gastrostomy, as determined endoscopically and/or radiologically.

Clinical success was not uniformly described, and was defined as ability to tolerate oral intake (for studies with GOO as an indication) or the successful achievement of ERCP through stent. Other descriptions were recorded when available.

Adverse events were categorized following the ASGE AE lexicon [11]. When included studies did not follow the ASGE lexicon, two authors (GA and BK) categorized adverse events conforming them to ASGE lexicon.

Data extraction

Two reviewers (GA and BK) independently extracted data from each study considered includable in the analysis, with any disagreements resolved by discussion.

The following data were recorded: study characteristics (author, publication year, study design, geographical area), number of patients fulfilling inclusion criteria; demographics (age, sex distribution); procedural characteristics (indication, type of sedation, use of antibiotics, echo-endoscope, technique used, type of LAMS, procedure length, failure rate and salvage method if any). In studies with different categories of patients (i.e. surgical patients), only data regarding patients undergoing the procedure of interest were extracted. The following outcomes of interests were recorded when available: technical success, clinical success, adverse events rate, stent failure, and migration rates.

Quality assessment

The quality of each study included in the quantitative synthesis was assessed by two independent reviewers (GA and BK) using the Methodological Index for Non-Randomized Studies (MINORS) [12]. See *Table S1*. Disagreements were resolved by discussion. In subanalyses, study quality was considered poor (score 5 or less), fair [6–10] or good (11 or more), as previously reported [13].

Statistical analysis

The primary outcome was pooled technical success rate and pooled clinical success rate, separately expressed for different indications, and pooled adverse events rate, stratified by severity (mild/moderate vs severe/fatal). Rates of events were expressed as proportions for all studies and used to calculate pooled technical success rate, pooled clinical success and pooled adverse events rate.

After data extraction, 95% confidence intervals of event rates for each study were calculated using exact methods and assuming a Poisson distribution. A meta-analysis of available studies was undertaken using the software package Comprehensive Meta- Analysis (Biostat, Englewood, New Jersey, USA) and a random-effects

Please cite this article as: G. Antonelli, B. Kovacevic and J.G. Karsensten et al., Endoscopic ultrasound-guided gastro-enteric anastomosis: A systematic review and meta-analysis, Digestive and Liver Disease, https://doi.org/10.1016/j.dld.2020.04.021

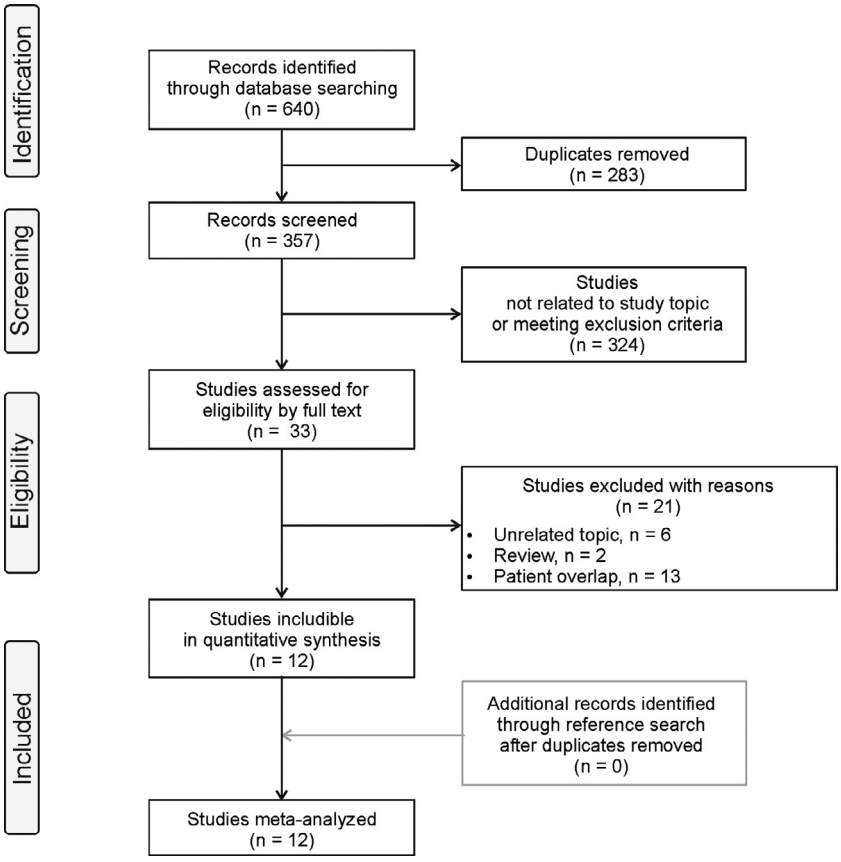

Fig. 1. PRISMA flowchart for screening and eligibility process.

model was chosen to consider variation (heterogeneity) across studies, if present. The amount of heterogeneity was quantified by means of the I^2 statistic. Publication bias was assessed using the Begg and Mazumdar test [14]. $P < 0.05$ was considered statistically significant.

Before conducting the statistical analysis, we *a priori* decided to explore eventual heterogeneity through a leave-one-out sensitivity analysis, by iteratively removing 1 study at a time to confirm that our findings were not driven by any single study.

Results

Study identification and selection

Primary search of the 4 databases retrieved 640 studies. After duplicates were removed, a total of 357 studies were identified and screened (see Fig. 1). Three hundred twenty-four studies were not related to the study topic or met one of the exclusion criteria. Thirty-three studies were further assessed for eligibility through full text examination, and 21 were excluded for not meeting all the inclusion / exclusion criteria; reasons for exclusion were recorded (See Fig. 1). Twelve studies [5,6,8,15–23] reporting on 290 patients of interest (see Table 1) were finally included in the quantitative synthesis through meta-analysis for describing patients undergoing EUS-guided positioning of LAMS for the creation of an enteric anastomosis.

The most frequent indication for procedure was GOO [8,16,18,19,21–23], both malignant or benign, followed by EDGE [5,17,20]. Direct puncture was the most employed technique (68.2% of procedures), and the majority of procedures were gastro-enteric anastomosis (83.1% of procedures). The majority of procedures (94.1%) were performed using a 15 mm Axios (Boston Scientific, USA) LAMS. Mean procedure time was 63.5 ± 35.7 min, and mean length of hospital stay was 4.9 ± 2.7 days. Further details are available in Table 2.

References of included studies were screened with the aim of eventually retrieving additional studies, but no further evidence was found.

Meta-analysis

Pooled technical success

When studies reporting technical success were pooled together (12 studies, 290 patients)(5, 6, 8, 15–23), the pooled technical success rate was 93.5% [95% Confidence Interval (CI) 89.7 - 96%] with no heterogeneity ($I^2 = 0\%$) and no publication bias (Begg and Mazumdar Kendall's $\tau = 0.09$ [$p = 0.68$]). See Fig. 1.

When only studies (7 studies, 179 patients) [8,16,18,19,21–23] with GOO as indication to gastro-enteric anastomosis were considered, pooled technical success rate was 92% [95% CI 86.9 – 95.3%], with no heterogeneity ($I^2 = 0\%$) and no publication bias ($\tau = 0.04$ [$p = 0.88$]). When considering only studies (3 studies, 78 patients) [5,17,20] reporting on patients undergoing EDGE, pooled technical success rate was 97.4% [95% CI 90.1 – 99.3%], with no heterogeneity ($I^2 = 0\%$) and no publication bias ($\tau = 0.2$ [$p = 0.71$]).

The main reported reason for technical failure was LAMS misdeployment, usually recognized immediately and treated endoscopically with deployment of a second LAMS, via EUS or NOTES or of a FCSEMS across the defect. Other endoscopic salvage methods included defect closure with OTSC or deployment of an intraluminal FCSEMS without defect closure.

When patients initially scheduled for EUS-GEA were not able to complete the procedure, the most common reasons were: inability to visualize the enteric limb on EUS; inappropriate positioning of

Please cite this article as: G. Antonelli, B. Kovacevic and J.G. Karsensten et al., Endoscopic ultrasound-guided gastro-enteric anastomosis: A systematic review and meta-analysis, Digestive and Liver Disease, https://doi.org/10.1016/j.dld.2020.04.021

Table 1
Characteristics of included studies.

First author, year	Setting	Country	Indications	Techniques	Age, #mean *median	Male, n (%)	Sample size (N)	Technical success (N,%)	Clinical success (N,%)	Adverse events (N,%)
Amateau 2018	Unicentric	Minnesota, USA	Reversal of Roux-en-Y (malnutrition, ERCP, obstruction) (100%)	Direct: 93% Balloon: 0% Other: 7%	53.3 (8.5) #	4 (26.6%)	15	15 (100%)	12 (80%)	3 (20%)
Brewer Gutierrez 2018	Multicentric	Baltimore, Seattle, Philadelphia, Jacksonville, USA; Aarhus, Denmark; München, Germany	Afferent Loop Syndrome (100%)	Direct: 100%	64.2(10.3) #	8 (44.4%)	18	18 (100%)	18 (100%)	3 (17%)
Brewer Gutierrez 2017	Multicentric	Baltimore, Jacksonville, Seattle, Chapel Hill, USA	Concurrent GOO and biliary obstruction (100%)	Direct: 71% Balloon: 29%	64,6 (12.5) #	3 (42.8%)	7	7 (100%)	7 (100%)	0
Bukhari 2018	Multicentric	Baltimore, Philadelphia, Jacksonville, Seattle, Washington, USA; Aarhus, Denmark	EDGE (100%)	Direct: 100%	52.5 (13.4) #	3 (10%)	30	30 (100%)	n/a	2 (7%)
Chen 2018	Multicentric	Baltimore, Boston, Jacksonville, Chapel Hill, Seattle, USA; Montreal, Canada; Aarhus, Denmark	GOO: Malignant (66.2%) Benign (33.8%)	Direct: 70% Balloon: 30%	63 (11.7) #	41 (55.4%)	74	69 (93%)	68 (92%)	5 (7%)
Ge 2019	Unicentric	Boston, USA	GOO: Malignant (100%)	Direct: 100%	66,4 (9.2) #	9 (40.9%)	22	22 (100%)	20 (91%)	5 (23%)
Itoi 2016	Not specified	Tokyo, Japan; Mumbai, India; Hongkong, China; San Francisco, USA	GOO: Malignant (100%)	Double Balloon: 100%	68 (46–89) *	10 (50%)	20	18 (90%)	18 (90%)	2 (10%)
James 2018	Unicentric	Chapel Hill, USA	EDGE (100%)	Direct: 100%	55 (3.2)	4 (21%)	19	19 (100%)	19 (100%)	0
Kedia 2018	Multicentric	Dallas, Jacksonville, Philadelphia, New York, USA	EDGE (100%)	Direct: 100%	56 (35–82) *	4 (13.8%)	29	28 (97%)	28 (97%)	n/a
Perez Miranda 2017	Multicentric	Valladolid, Vigo, Spain; New York, Denver, USA; Marseille, France	GOO: Malignant (68%) Benign (32%)	Direct: 24% Balloon: 36% Other: 40%	63,9 #	11 (44%)	25	22 (88%)	21 (84%)	3 (12%)
Tyberg 2016	Multicentric	New York, San Francisco, Chapel Hill USA; Valladolid, Spain	GOO: Malignant (65%) Benign (35%)	Direct: 11% Balloon: 50% Other: 30%	66,2 #	11 (42.3%)	26	24 (92%)	24 (92%)	3 (12%)
Urrehman 2018	Unicentric	Singapore	GOO: Malignant (100%)	Balloon: 100%	61,5 (53.83) *	2 (40%)	5	5 (100%)	4 (80%)	0

Please cite this article as: G. Antonelli, B. Kovacevic and J.G. Karsensten et al., Endoscopic ultrasound-guided gastro-enteric anastomosis: A systematic review and meta-analysis, Digestive and Liver Disease, https://doi.org/10.1016/j.dld.2020.04.021

Table 2
Characteristics of patients and procedures.

Tatal patients	290
Men, n (%)	110 (37,9%)
Age, mean (SD)	62,9 ± 28.7
Follow up[#], mean (SD)	134±68.2
Indication to EUS	
Malignant GOO	137 (47.2%)
Benign GOO	44 (15.2%)
ERCP through stent	81 (27.9%)
Afferent loop syndrome	18 (6.2%)
Other/Missing	10 (3.4%)
Technique	
Direct puncture	198 (68.2%)
Single Balloon	51 (17.5%)
Other/Missing	20 (6.9%)
Anastomosis	19 (6.5%)
Gastro-eneric	241 (83.1%)
Gastro-gastric	48 (16.5%)
Entero-enteric	1 (0.3%)
LAMS	
Hot Axios, 15/10mm	172 (59.3%)
Cold Axios, 15/10mm	101 (34.8%)
Other/Missing	17 (5.9%)
Procedure Time[*], mins, mean (SD)	63,5 ± 35,7
Hospitalization length[§], days, mean (SD)	4,9 ± 2,7
Failure rate n (%)	12 (4,1%)

[#] available for 11 studies.
[*] Available for 8 studies.
[§] available for 7 studies.

the enteric limb (i.e. too far) to safely deploy the LAMS; presence of peritoneal carcinomatosis between stomach and enteric limb.

Pooled clinical success

When analysing clinical success, 11 studies reported this outcome for 260 patients [5,6,8,15,16,18–23]. Pooled clinical success rate from all studies was 90.1% [95% CI 85.5– 93.4%] with no heterogeneity ($I^2 = 0\%$) and no publication bias ($\tau = 0.2$ [$p = 0.39$]). See **Fig. 2**.

When analysing only studies (7 studies, 179 patients) [8,16,18,19,21–23] reporting on patients with GOO, pooled clinical success rate was 89.9% [95% CI 84.4– 93.6%] with no heterogeneity ($I^2 = 0\%$) and no publication bias ($\tau = 0.1$ [$p = 0.44$]). In GOO patients, clinical failure was considered as inability to tolerate any oral intake after a technically successful procedure. In these cases, a second LAMS was sometimes used as a salvage procedure, as well as the positioning of an endoscopic or surgical PEG.

Only two studies [17,20] reporting on patients undergoing EDGE reported a definition for clinical success as "success in performing ERCP through the LAMS". The pooled clinical success rate for these 2 studies was 97.3% [95% CI 87.8– 99.5%] with no heterogeneity ($I^2 = 0\%$) and no publication bias ($\tau = -0.1$ [$p = 0.9$]). Failure in performing ERCP through the LAMS was mainly due to dislodgment of the LAMS during ERCP. Methods used to minimize this risk include allowing time for the maturation of the fistula (1–4 weeks), LAMS fixation with clips or endo-suturing devices and lubrication of the duodenoscope.

Adverse events

Pooled estimate of overall adverse event rate from 11 studies (261 patients) [5,6,8,15–19,21–23] was 11.7% [95% CI 8.2– 16.6%] with no heterogeneity ($I^2 = 0\%$) and no publication bias (Begg and Mazumdar Kendall's $\tau = -0.2$ [$p = 0.19$]). See Fig. 3.

Stent misdeployment, when specifically addressed, was usually considered amongst adverse events and classified using the ASGE Adverse Events Lexicon [11]. Stent misdeployments were usually managed endoscopically by positioning a bridge SEMS.

We then sub-categorized adverse events in two groups, mild/moderate and severe/fatal. Pooled mild/moderate adverse events rate was 10.6% [95% CI 7 – 15.6%], while pooled severe/fatal adverse events rate was 2.9% [95% CI 1.4 – 6%] with low ($I^2 = 3.4\%$) and no heterogeneity ($I^2 = 0\%$), respectively and no ($\tau = 0.1$ [$p = 0.27$]; $\tau = -0.8$ [$p = 0.39$], respectively) publication bias. See Fig. 4.

Overall, two fatalities (0.6% of total included patients) occurred across all included studies, in two very fragile patients with long standing malignancy and peritoneal carcinomatosis.

Sensitivity analyses

To evaluate the strength of the results, we performed a leave-one-out sensitivity analysis by iteratively removing one study at a time and repeating calculations of pooled outcomes. The pooled estimates remained stable, indicating that our results were not mainly influenced by any single study and that similar results can be drawn by leaving out any of the studies included.

Quality assessment

Included studies were all retrospective in nature. Using the Methodological Index for Non-Randomized Studies (MINORS) Scale, no study resulted as "good" (11 or above). Only one study scored as "poor", and all the other studies were rated "fair", and therefore sensitivity analysis according to study quality was not deemed necessary. See *Table S1* for details.

Discussion

To the best of our knowledge, this is the first comprehensive pooled analysis of available literature that presents an overall picture of efficacy and safety of EUS-guided enteric anastomosis. Although included studies were all retrospective in nature, meta-analysis showed fairly homogeneous results, without apparent publication bias.

Overall, technical success of the procedure in expert hands was obtained in over 90% of cases, and this high rate remained constant also after performing sub analysis for procedure indication and sensitivity analysis. Furthermore, the rare reported technical failures appear to be closely related to LAMS mis-deployment [18,21] and are usually amenable by endoscopic treatment with OTSC or FCSEMS positioning, with a very low rate of severe adverse events. Although we originally intended to pool and compare outcomes of different EUS-anastomosis techniques, current literature is limited and does not permit this kind of sub-analyses. Only one study so far [18] was conceived with the intention of comparing the two main techniques (direct access and balloon assisted). Interestingly, in this retrospective multicentre study, the direct access technique yielded similar technical and clinical outcomes, while showing a significantly shorter procedure time. Direct access is usually perceived as at higher risk of inadvertently puncturing the colon or other adjacent organs, but the authors point out how jejunal inflation with a methylene blue dyed solution and the usage of a "finder" needle before stent insertion minimises this risk. Surely, future studies must be designed to prospectively compare these techniques and should be powered accordingly.

Similarly, a high pooled rate of clinical success was observed, and this remained stable also when sub-analysing for different procedure indications. First, when treating GOO, EUS-GEA seems to be a faster and less invasive way of restoring bowel continuity compared to surgery. Patients undergoing this endoscopic procedure are usually considered unfit for surgery, and across studies this has been highlighted as a possible selection bias, likely representing a more fragile group of patients. However, considering the notwithstanding high clinical success rate of the procedure, we believe that this aspect should actually strengthen and broaden indi-

Please cite this article as: G. Antonelli, B. Kovacevic and J.G. Karsensten et al., Endoscopic ultrasound-guided gastro-enteric anastomosis: A systematic review and meta-analysis, Digestive and Liver Disease, https://doi.org/10.1016/j.dld.2020.04.021

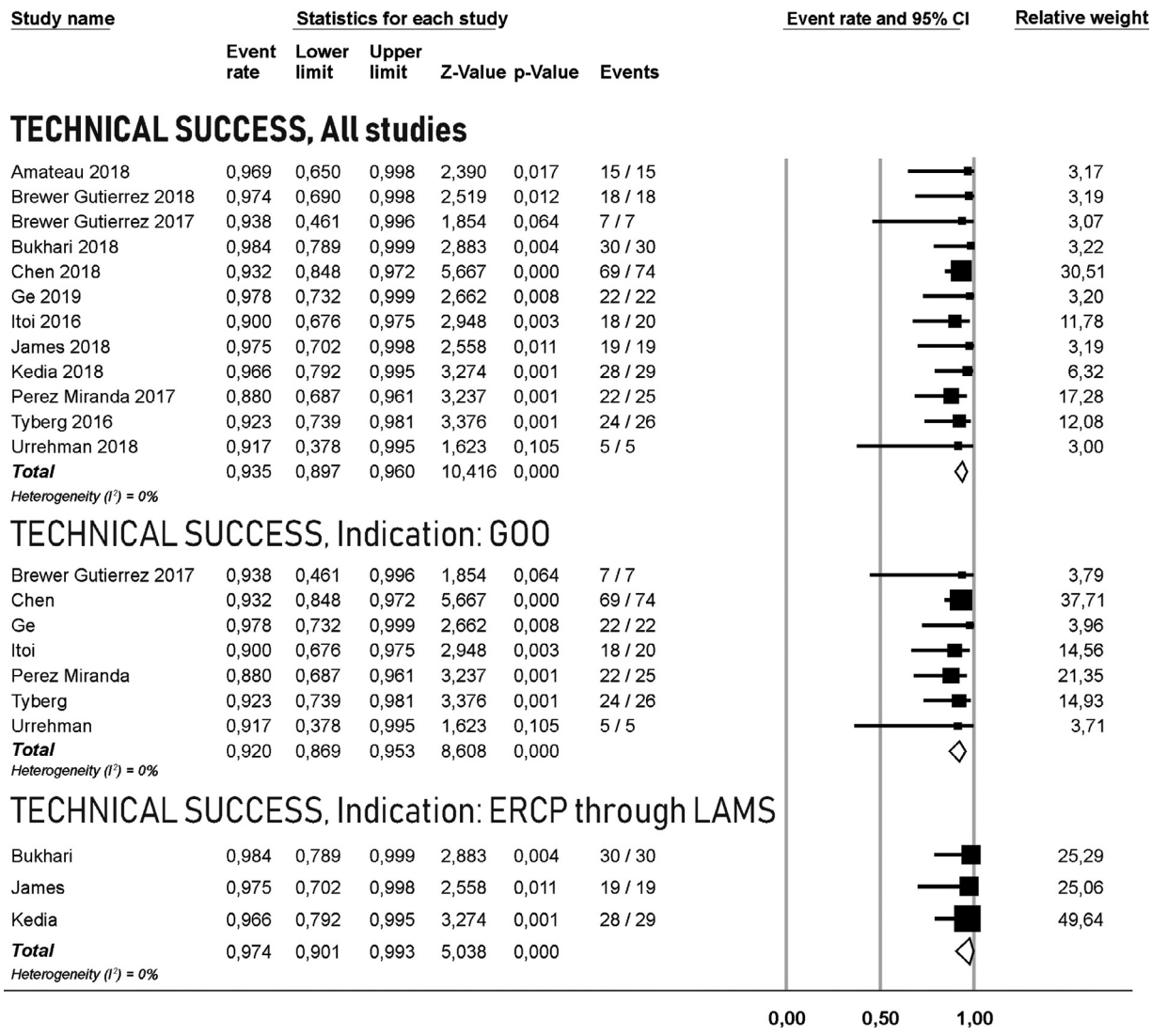

Fig. 2. Forest plots for pooled technical success rates.

cations to the procedure. Furthermore, EUS-GEA permits a rapid return to oral feeding and chemotherapy, critical issues in seriously ill, oncological patients. Only one study [19] was designed comparing EUS-GEA with enteral stenting, the current standard of care in patients with GOO unfit for surgery. Whilst showing a comparable, high, technical success, rates of clinical success and stent patency were significantly in favour of EUS-GEA using LAMS. In particular, a reduced reintervention rate coupled with a reduced number of reinterventions per patient, is a clue towards the possible favourable cost-effectiveness of this technique, albeit a specific analysis on this topic is still lacking. It must be noted that the definition of clinical success is heterogeneous amongst studies including patients with GOO. The general definition was "ability to tolerate at least a liquid diet", some studies included a time-span (30 or 90 days), and only one study [8] included a validated scoring system for GOO symptoms. We believe that the inclusion of the GOOSS score [24] in future studies is desirable to better evaluate clinical success in GOO patients undergoing EUS-GEA, as it is a way to objectivate and compare GOO symptoms, possibly underlining subtle differences that could otherwise go unnoticed. Furthermore, we believe it will be important to analyse procedure performance and indications between patients with malignant and benign GOO, a sub-analysis that was not possible with currently available literature. This is also important in light of the possible different reasons for technical failure, that appear to be more common in patients with malignancies (peritoneal carcinomatosis). Long-term follow up in patients with benign GOO treated with EUS-GEA could help to understand if this approach is a valid alternative to surgery also in fit patients with a potentially long life expectancy. The availability of improved, larger diameter LAMSs could also improve symptom relief and patency duration.

When considering clinical success of EDGE, successful ERCP rate was high, and the most frequent reason for failure was LAMS dislodgement during procedure, usually safely salvaged endoscopically. It is still unclear whether ERCP through the LAMS is preferable during the same session or after a selected time-span, and whether this difference can affect outcomes. The different nature of included studies did not permit pooled comparisons between EDGE and other techniques. However, in included studies, EDGE seems to compare favourably both to enteroscopy-[17] and laparoscopy-assisted [20] ERCP, showing higher success rates and shorter procedure times, while maintaining a similar safety profile. These initial promising results should be confirmed by future studies, that should also focus on the post-procedural management of these patients. In published studies, fistula closure is still heterogeneously managed. A preferred method for fistula closure is treat-

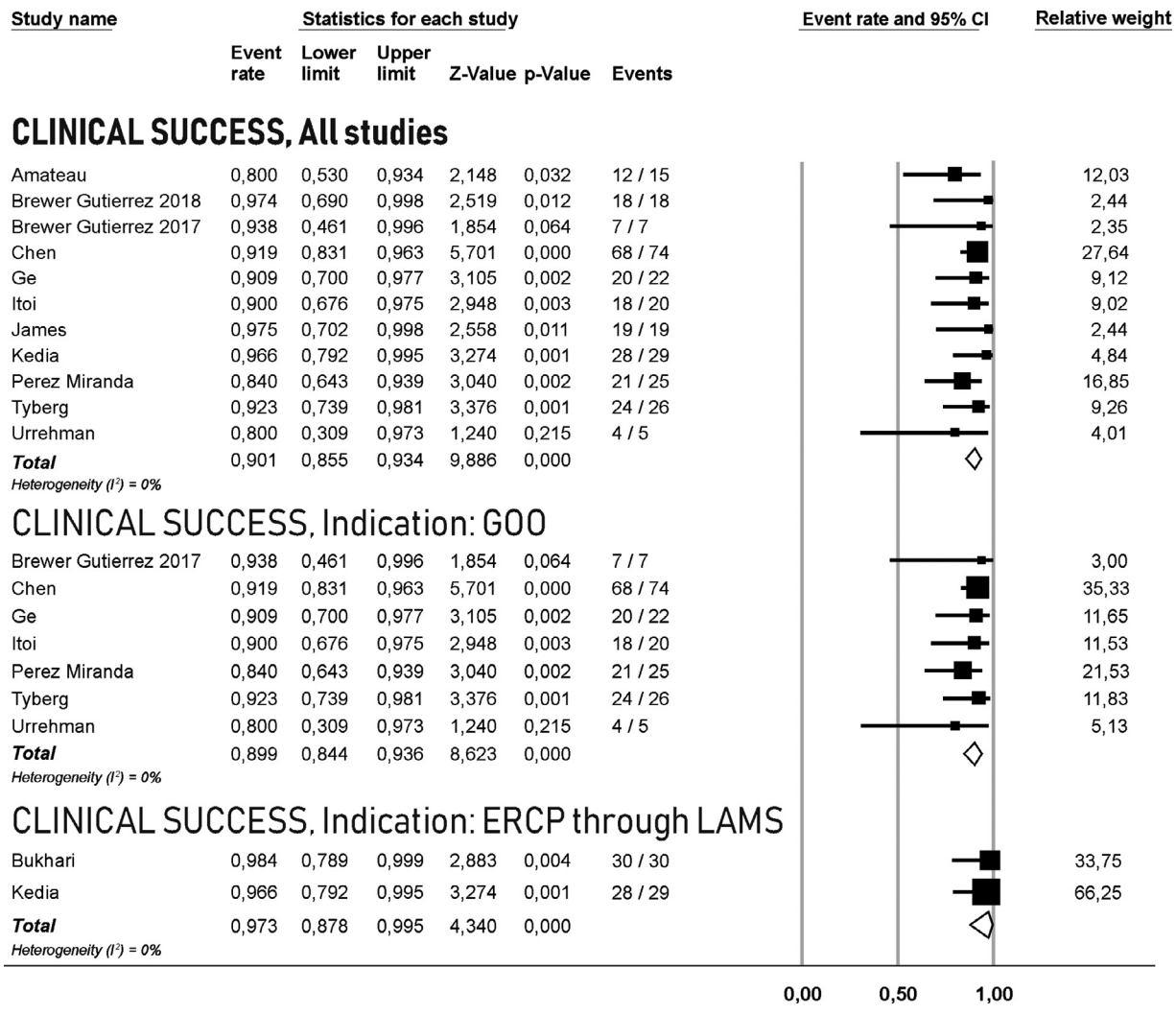

Fig. 3. Forest plots for pooled clinical success rates.

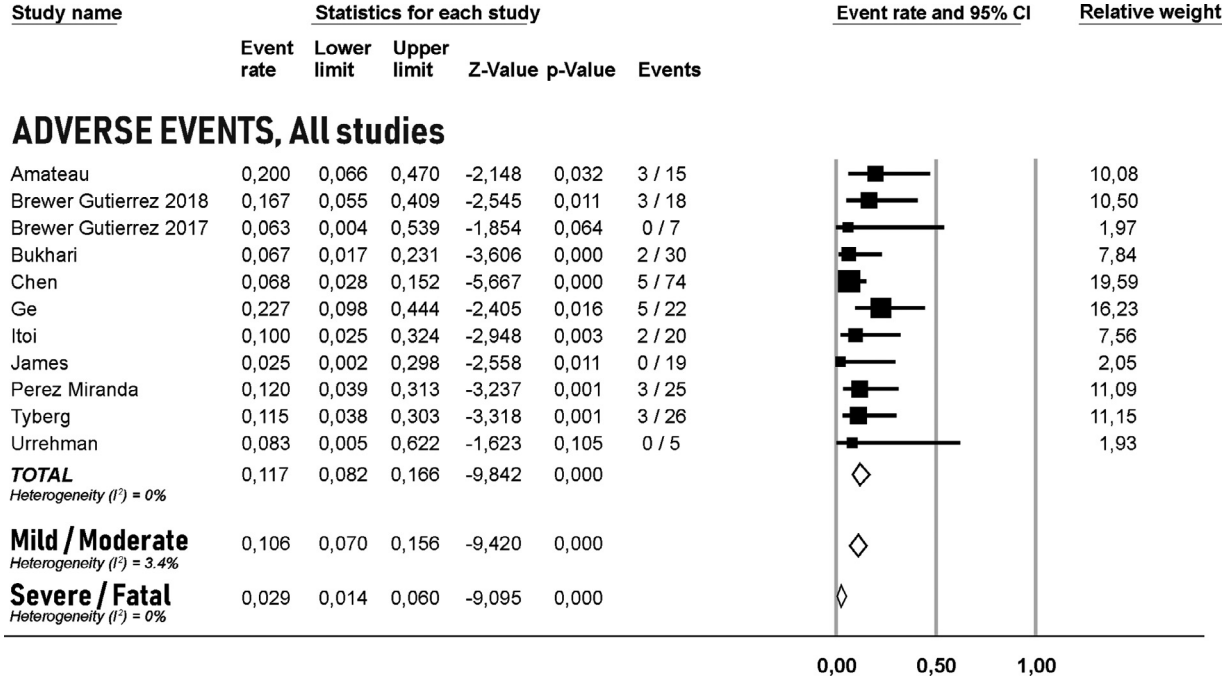

Fig. 4. Forest plots for pooled adverse events rates.

Please cite this article as: G. Antonelli, B. Kovacevic and J.G. Karsensten et al., Endoscopic ultrasound-guided gastro-enteric anastomosis: A systematic review and meta-analysis, Digestive and Liver Disease, https://doi.org/10.1016/j.dld.2020.04.021

ment with Argon followed by a spontaneous closure, while other fistulas are endoscopically closed with clips or suturing devices. While the preferred technique is still unclear, follow up data suggest an overall satisfactory fistula closure rate.

Pooled rate of adverse events was low, and the majority were graded low/moderate following the ASGE lexicon. Only two fatalities occurred across included studies. Both cases were reported to occur in patients developing peritonitis after LAMS misdeployment. Both patients had long-standing malignant disease and peritoneal carcinomatosis [21,22]. This should reassure on the safety profile of the procedure, although the technique has not yet been reported outside of selected, tertiary referral centres. A higher rate could be expected in a real-life clinical setting and is a further urge for the standardisation of procedure technique.

Mild/moderate adverse events were mainly related to stent misdeployment during the procedure, usually salvaged with positioning of a second stent, a FCSEMS or defect closure with OTSC. It would be of great interest to investigate the rate of adverse events across different techniques in adequately powered studies, as well as the potential role of other patient- and procedure-related variables. Other common mild/moderate adverse events included postprocedural abdominal pain, safely treated conservatively. In studies comparing EUS-GEA with surgical procedures [21] or enteral stenting [19], EUS-GEA patients experienced significantly less adverse events and this is especially meaningful since these patients are usually poor surgical candidates. Indeed, although laparoscopic GEA is a relatively safe and fast surgical procedure, it is still burdened by high rates of morbidity and mortality in patients with malignant GOO [25]. Furthermore, EUS-GEA can be an option in many patients with malignant GOO that are unable to undergo surgery, permitting a quicker recovery without the burden of incision-related infections and pain. No data are available comparing patency of the two approaches.

In conclusion, according to current literature, EUS-GEA seems to be a safe alternative to surgery in re-establishing bowel continuity. EUS-GEA is a technically challenging technique, that has shown promising results when performed by experienced operators. Technique standardisation and prospective studies are needed to strengthen indications and expand employment of the procedure.

Author contributions

GA, PV: conception and design; GA, BK, CH: extraction, analysis and interpretation of the data; GA, BK: drafting of the article; JGK, EK, GV, CH, PV: critical revision of the article for important intellectual content.

All authors read and approved the final version of the manuscript.

Declaration of Competing Interest

None to declare for any author.

Funding

No funding was obtained for this study

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2020.04.021.

References

[1] Siddiqui UD, Levy MJ. EUS-guided transluminal interventions. Gastroenterology 2018;154(7):1911–24.
[2] Binmoeller KF, Shah JN. Endoscopic ultrasound-guided gastroenterostomy using novel tools designed for transluminal therapy: a porcine study. Endoscopy 2012;44(5):499–503.
[3] Khashab MA, Kumbhari V, Grimm IS, Ngamruengphong S, Aguila G, El Zein M, et al. EUS-guided gastroenterostomy: the first U.S. clinical experience (with video). Gastrointest Endosc 2015;82(5):932–8.
[4] Mussetto A, Fugazza A, Fuccio L, Triossi O, Repici A, Anderloni A. Current uses and outcomes of lumen-apposing metal stents. Ann Gastroenterol 2018;31(5):535–40.
[5] James TW, Baron TH. Endoscopic ultrasound-directed transgastric ERCP (EDGE): a single-center US experience with follow-up data on fistula closure. Obes Surg 2018.
[6] Brewer Gutierrez OI, Irani SS, Ngamruengphong S, Aridi HD, Kunda R, Siddiqui A, et al. Endoscopic ultrasound-guided entero-enterostomy for the treatment of afferent loop syndrome: a multicenter experience. Endoscopy 2018;50(9):891–5.
[7] Khashab MA, Baron TH, Binmoeller KF, Itoi T. EUS-guided gastroenterostomy: a new promising technique in evolution. Gastrointest Endosc 2015;81(5):1234–6.
[8] Itoi T, Ishii K, Ikeuchi N, Sofuni A, Gotoda T, Moriyasu F, et al. Prospective evaluation of endoscopic ultrasonography-guided double-balloon-occluded gastrojejunostomy bypass (EPASS) for malignant gastric outlet obstruction. Gut 2016;65(2):193–5.
[9] Kovacevic B, Vilmann P, Karstensen JG. Gastric outlet obstruction syndrome due to an obstructed hepaticojejunostomy loop treated by one-step endoscopic ultrasound-guided gastroenterostomy. Endoscopy 2016;48(Supplement 01):E103–E1E4.
[10] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62(10):1006–12.
[11] Cotton PB, Eisen GM, Aabakken L, Baron TH, Hutter MM, Jacobson BC, et al. A lexicon for endoscopic adverse events: report of an ASGE workshop. Gastrointest Endosc 2010;71(3):446–54.
[12] Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 2003;73(9):712–16.
[13] Vanella G, Crippa S, Archibugi L, Arcidiacono PG, Delle Fave G, Falconi M, et al. Meta-analysis of mortality in patients with high-risk intraductal papillary mucinous neoplasms under observation. Br J Surg 2018;105(4):328–38.
[14] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50(4):1088–101.
[15] Amateau SK, Lim CH, McDonald NM, Arain M, Ikramuddin S, Leslie DB. EUS-Guided Endoscopic Gastrointestinal Anastomosis with Lumen-Apposing Metal Stent: feasibility, Safety, and Efficacy. Obes Surg 2018;28(5):1445–51.
[16] Brewer Gutierrez OI, Nieto J, Irani S, James T, Pieratti Bueno R, Chen YI, et al. Double endoscopic bypass for gastric outlet obstruction and biliary obstruction. Endosc Int Open 2017;5(9):E893–E8e9.
[17] Bukhari M, Kowalski T, Nieto J, Kunda R, Ahuja NK, Irani S, 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(3):486–94.
[18] Chen YI, Kunda R, Storm AC, Aridi HD, Thompson CC, Nieto J, et al. EUS-guided gastroenterostomy: a multicenter study comparing the direct and balloon-assisted techniques. Gastrointest Endosc 2018;87(5):1215–21.
[19] Ge PS, Young JY, Dong W, Thompson CC. EUS-guided gastroenterostomy versus enteral stent placement for palliation of malignant gastric outlet obstruction. Surg Endosc 2019.
[20] Kedia P, Tarnasky PR, Nieto J, Steele SL, Siddiqui A, Xu MM, et al. EUS-directed Transgastric ERCP (EDGE) Versus Laparoscopy-assisted ERCP (LA-ERCP) for Roux-en-Y Gastric Bypass (RYGB) Anatomy: a Multicenter Early Comparative Experience of Clinical Outcomes. J Clin Gastroenterol 2018.
[21] Perez-Miranda M, Tyberg A, Poletto D, Toscano E, Gaidhane M, Desai AP, et al. EUS-guided Gastrojejunostomy Versus Laparoscopic Gastrojejunostomy: an International Collaborative Study. J Clin Gastroenterol 2017;51(10):896–9.
[22] Tyberg A, Perez-Miranda M, Sanchez-Ocana R, Penas I, De La Serna C, Shah J, et al. Endoscopic ultrasound-guided gastrojejunostomy with a lumen-apposing metal stent: a multicenter, international experience. Endosc Int Open 2016;4(3):E276–EE81.
[23] Urrehman A, Khor CJ, Ka CY, Asokkumar R, Tan D. EUS-guided gastrojejunostomy using a lumen apposing metal stent in patients with symptomatic gastric outlet obstruction. Gastrointest Endosc 2018;87:AB359 (6 Supplement 1).
[24] Adler DG, Baron TH. Endoscopic palliation of malignant gastric outlet obstruction using self-expanding metal stents: experience in 36 patients. Am. J. Gastroenterol. 2002;97(1):72–8.
[25] Medina-Franco H, Abarca-Perez L, Espana-Gomez N, Salgado-Nesme N, Ortiz-Lopez LJ, Garcia-Alvarez MN. Morbidity-associated factors after gastrojejunostomy for malignant gastric outlet obstruction. Am Surg 2007;73(9):871–5.