# Endoscopic ultrasound-guided gastroenterostomy versus surgical gastrojejunostomy in treatment of malignant gastric outlet obstruction: Systematic review and meta-analysis



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#### ABSTRACT

**Background and study aims** Palliative treatment of malignant gastric outlet obstruction (GOO) has conventionally been with surgical gastrojejunostomy (SGJ). Advent of devices like lumen apposing metal stents has made endoscopic ultrasound-guided gastroenterostomy (EUS-GE) a potential alternative to SGJ for these patients. We performed a systematic review and meta-analysis of studies that compared outcomes of EUS-GE versus SGJ.

**Methods** We performed a comprehensive systematic search of multiple electronic databases and conference proceedings through January 2021 and identified six studies that compared outcomes of EUS-GE versus SGJ in the management of malignant GOO. The rates of technical success, clinical success, and AEs were analyzed, and pooled odds ratios were calculated using random effects model.

**Results** Six studies were included in our analysis with a total of 484 patients, of which 291 underwent EUS-GE and 193 underwent SGJ. The technical success rate of SGJ was superior to EUS-GE (OR=0.195; 95%Cl:0.054–0.702; P= 0.012;  $I^2=0$ ). The clinical success of EUS-GE was statistically similar to SGJ (OR=1.566; 95%Cl:0.585–4.197; P=0.372;  $I^2=46.68\%$ ). EUS-GE had significantly fewer AEs compared to SGJ (OR=0.295; 95%Cl:0.172–0.506; P<0.005;  $I^2=0$ ). Among studies which reported reintervention rates, EUS-GE was statistically similar to SGJ (OR=0.587; 95% Cl:0.174–1.979; P=0.390,  $I^2=54.91$ ). Minimal to moderate heterogeneity was noted in the analyses.

**Conclusions** EUS-GE has equivalent clinical success and reintervention rates, but significantly lower adverse events compared to SGJ. When feasible, EUS-GE appears to be an effective and safe alternative to SGJ for palliative management of malignant GOO.

# Introduction

The primary approach for managing malignant gastric outlet obstruction (GOO) is palliation of symptoms [1]. Historically, the surgical gastrojejunostomy (SGJ) was the standard of care and most common intervention performed, with a more recent transition toward less invasive procedures like enteral self-expandable metal stents (SEMS) or decompressive venting gastrostomy [2–4]. However, patients with malignant GOO are not always optimal surgical candidates due to sequelae associated with cancer and GOO. These patients often suffer from malnutrition, electrolyte abnormalities, and poor wound healing. Their poor nutritional status renders them poor operative candidates. Moreover, the invasive nature of SGJ poses a risk for serious complications including bleeding, gastroparesis, perioperative infections, and increased morbidity which can delay recovery and subsequent chemotherapy treatments [5]. Therefore, alternative approaches for the management of GOO have been developed.

An endoscopic approach using enteral SEMS has shown better short-term outcomes and decreased complication rates compared to SGJ in palliative management of malignant GOO [3,5,6]. However, one of the main drawbacks is the lack of long-term benefit due to recurrent obstruction as a result of tumor ingrowth/overgrowth [3]. The development and availability of lumen apposing metal stents (LAMS) has allowed for the emergence of endoscopic ultrasound-guided gastroenterostomy (EUS-GE). EUS-GE is a novel procedure that has become increasingly accepted as a treatment approach for malignant GOO [7,8]. The procedure entails the deployment of a LAMS across a fistulous tract created between the gastric and the enteral lumen under EUS guidance, allowing for direct access of the small bowel from the gastric lumen and a bypass of the GOO [9]. Studies have demonstrated the safety, efficacy, and feasibility of EUS-GE in patients with malignant GOO [10–12].

With various options for palliation of symptoms associated with malignant GOO, the selection of the optimal treatment approach remains controversial. EUS-GE, being a less invasive endoscopic procedure, has the potential of offering a longterm palliative benefit in patients with malignant GOO as opposed to enteral SEMS [13, 14]. Few studies comparing the outcomes of EUS-GE and SGJ in this patient population have been performed [15–20]. The aim of our study was to perform a systematic review and meta-analysis of the available literature that directly compared outcomes including clinical success, technical success, adverse events (AE), and recurrence or reintervention rates, between EUS-GE and SGJ for malignant GOO symptom palliation as new data emerges on this novel endoscopic procedure.

# Materials and methods

This systematic review was performed in accordance with Cochrane Handbook for Systematic Reviews of Interventions [21]. It is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22].

# Data sources and search strategies

A comprehensive search of several databases from inception to January 31, 2021, limited to English language and excluding animal studies, was conducted. The databases included Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for studies describing EUS-GE, SGJ and GOO. The actual strategy listing all search terms used and how they are combined is available in **Appendix 1**.

The keywords used in the search included a combination of EUS guided gastroenterostomy, gastrojejunostomy (GJ), laparoscopic, open, surgical GJ, malignant gastric outlet obstruction. Two authors (SB, AG) independently reviewed the titles and abstracts of studies identified in the primary search and excluded studies that did not address the research question, based on pre-specified exclusion and inclusion criteria. The full text of the remaining articles was then reviewed to determine whether it contained relevant information. Any discrepancy in article selection was resolved by consensus and in discussion with a co-author (RK). The bibliographic sections of the selected articles, as well as the systematic and narrative articles on the topic, were manually searched for additional relevant articles.

### Study selection

Studies considered in this meta-analysis were cohort studies that met the following inclusion criteria: 1) Study population consisting of majority of the patients with malignant GOO; 2) Comparison of cohorts who underwent SGJ versus EUS-GE; 3) Reported outcomes which included technical success, clinical success, AE, and recurrence and/or reintervention rates; and 4) Sample size of 10 patients or more. We excluded: 1) studies that did not directly compare outcomes of EUS-GE and SGJ; 2) studies that were in non-English language or on animal; and 3) letters to the editor, case reports, editorials, and review articles. If multiple publications were identified from the same cohort, then most recent and / or most appropriate comprehensive report was included.

# Data extraction and quality assessment

After relevant studies were identified, two authors abstracted the data on study characteristics, relevant outcomes of interest into a standardized form. The risk of bias and study quality was independently assessed by two authors (SB, AG) using the Newcastle-Ottawa scale (NOS) for cohort studies [23]. Using the scale, the studies were assigned scores under three broad perspectives: (1) Selection (4 questions); (2) comparability of study groups; and (3) ascertainment of the outcome of interest (3 questions). All questions received a score of one except for comparability which could get a maximum of 2. Studies with a total score  $\geq 8$ , 5 to 7, and  $\leq 5$  were considered high, medium, and low-quality studies, respectively. Any discrepancies in data abstraction and quality assessment were resolved by joint assessment of the original articles by two authors (SB, RK).

#### Outcomes assessment

The primary outcome of the current meta-analysis was to compare rates of technical success and clinical success of EUS-GE vs SGJ. Secondary outcomes were AE and recurrence and/or reintervention rates of EUS-GE vs SGJ.

Technical success was defined as successful creation of a gastroenterostomy during the procedure and clinical success was defined as ability tolerate at least liquid diet after the procedure. Recurrence was defined as recurrence of symptoms due to GOO and reintervention was defined as any repeat procedure done due to patients' recurrence of symptoms or as a consequence of failure or AE from the primary procedure. AEs were defined as complications or adverse outcomes related to procedure or stent. AEs were defined and classified based on American Society of Gastrointestinal Endoscopy lexicon or Clavein-Dindo classification [24, 25].

# Statistical analysis

We used meta-analysis techniques to calculate the pooled rates of outcomes using random effects model described by DerSimonian and Laird [26]. Odds ratios comparing the outcome of interest between two procedures was calculated. The pooled odds ratios comparing the rates of outcomes between the two groups with 95% confidence intervals and heterogeneity was measured.

Heterogeneity was calculated using Cochran's Q statistical test and I<sup>2</sup> statistic. The Q-statistic provides a test of the null hypothesis that all studies in the analysis share a common effect size. If all studies shared the same effect size, the expected value of Q would be equal to the degrees of freedom (the number of studies minus 1). When the expected value of Q exceeds the degrees of freedom, the null hypothesis is rejected and variations across the studies and heterogeneity is accepted to exist. I<sup>2</sup> statistic estimates the proportion of total variation across studies that is related to heterogeneity rather than by chance. Values of < 30%, 30% to 60%, 61% to 75%, and >75% were considered suggestive of low, moderate, substantial, and considerable heterogeneity, respectively [27]. P<0.05 was considered to be statistically significant. If there were ≥ 10 studies included in the meta-analysis, we planned to assess for publication bias qualitatively, by visual inspection of a funnel plot and quantitatively, by the Egger test. All statistical analyses were performed by using Comprehensive Meta-Analysis (CMA) software, version 3 (BioStat, Englewood, New Jersey, United States).

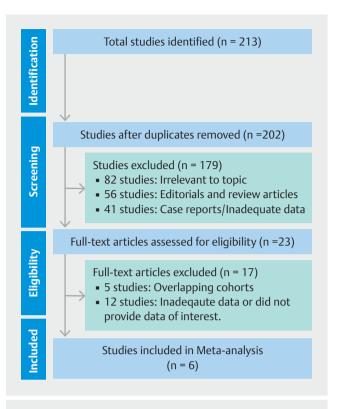
# Results

A total of 213 studies were identified by our search criteria. After removing duplicates, 202 studies were screened based on titles and abstracts. One hundred and seventy-nine studies were excluded due to various reasons which include irrelevance to topic, editorials and review articles, inadequate data, and case reports. After above exclusions 23 studies were reviewed. Five studies were excluded due to overlapping cohorts and 12 studies were excluded due to lack of specific data of interest.

Six studies that directly compared EUS-GE and SGJ fulfilled our inclusion criteria and were included in this meta-analysis [15–20]. ► Fig. 1 illustrates the study identification and selection process.

# Characteristics and quality of included studies

A total of six retrospective comparative studies were included in the analysis [15–20]. Three studies were international multicenter studies [16, 18, 20] and three were single center [15, 17, 19]. The three single-center studies were conducted in the Uni-



**Fig.1** Flowchart summarizing study selection process.

ted States [15, 17, 19]. The International multicenter studies included centers from the United States, Japan, Belgium, France, and Spain. While all the studies compared the outcomes between EUS-GJ vs SGJ, one study also compared outcomes of enteral stenting for the treatment of GOO [20]. Study characteristics of each included study have been summarized in  $\blacktriangleright$  Table 1. Overall outcomes of EUS-GE and SGJ of all the studies included in the meta-analysis has been illustrated in  $\triangleright$  Fig. 2.

# **Primary outcomes**

The technical success rate of EUS-GE was inferior compared to SGJ with OR = 0.195 (95%CI: 0.054–0.702; P = 0.012; Q = 1.909; I<sup>2</sup> = 0) and this was statistically significant. The calculation of heterogeneity was minimal with Q value within degrees of freedom and I<sup>2</sup> was 0 (**> Fig. 3**).

The Odd's ratio for the rate of clinical success between EUS-GE and SGJ trended toward favoring EUS-GE, but statistically insignificant (OR = 1.566; 95%CI: 0.585–4.197; P= 0.372; Q= 9.37; I<sup>2</sup>= 46.68%), However, a wide confidence interval of 0.6 to 4.2 demonstrates uncertainty regarding this outcome. Heterogeneity was moderate (**> Fig. 4**).

# Secondary outcomes

The rate of AEs was lower in the EUS-GE group compared to the SGJ group (OR = 0.295; 95% CI: 0.172–0.506; P<0.005; Q = .40: I<sup>2</sup>=0) and was statistically significant. Heterogeneity was minimal (**> Fig.5**).

Among the five studies which reported recurrence and/or reintervention rates, there was no statistically significant differ-

Study/ year	Center/ countries	Study type/ time period/ publication type	Interven- tion	Total patients (N)	Mean age (y)	Type of surgery
Khashab et al/	Multicenter/	Retrospective cohort/	EUS-GE	30	70	Open-GJ
2016	USA, Japan	2006–2015/ Manuscript	SGJ	63	68	
Perez-Miranda	Multicenter/	Retrospective cohort/	EUS-GE	25	63.9	Lap-GJ
et al/ 2017	Spain, USA, France	2010–2015/ Manuscript	SGJ	29	75.8	
Widmer et al/ 2019	Single center/ USA	Retrospective cohort/ EUS-GE 10		10	63	Open-GJ &
		2015–2018/ Abstract	SGJ	14	68	lap-GJ
Marya et al/	Multicenter/	Retrospective cohort/	EUS-GE	172	62.4	Unspecified
2020	USA, Belgium	2005–2019/ Abstract	SGJ	39	63.9	
Bondi et al/ 2020	Single center/	Retrospective cohort/	EUS-GE	18	64	Unspecified
	USA	2000–2019/ Abstract	SGJ	34	61.3	
Kouanda et al/ 2021	Single center/	Retrospective cohort/	EUS-GE	36	70.4	Open-GJ
	USA	2014–2020/ Manuscript	SGJ	14	71.5	

#### ► Table 1 Characteristics of studies involved in meta-analysis comparing EUS-GE vs SGJ.

EUS-GE – endoscopic ultrasound-guided gastroenterostomy; SGJ – surgical gastrojejunostomy; Lap –laparoscopic.

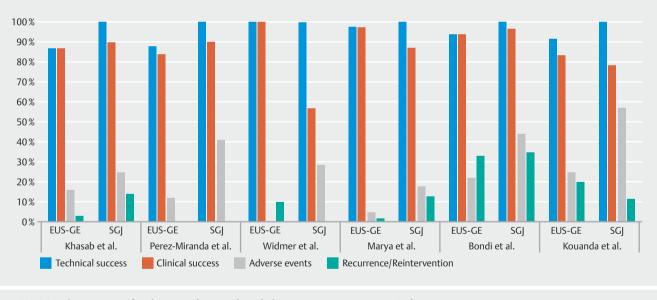


Fig.2 Study outcomes of endoscopic ultrasound-guided gastroenterostomy vs surgical gastrojejunostomy.

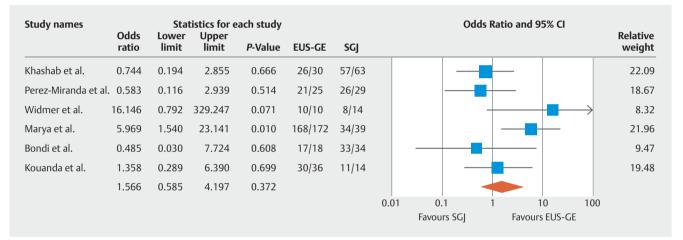
ence in the overall recurrence/reintervention rates between EUS-GE vs SGJ (OR=0.587; 95%CI: 0.174–1.979; P=0.390, Q= 8.87; I<sup>2</sup>=54.91). Heterogeneity was moderate (**> Fig. 6**).

# Risk of bias and study quality assessment

Risk of bias and quality assessment of the involved retrospective cohort studies were done using NOS. Four studies were deemed to be high quality [16, 17,19,20] and two were deemed medium quality [15, 18]. The quality assessment of each study has been detailed in **Supplementary Table 1**. Assessment of publication bias was performed despite the limited number of studies using a funnel plot and Egger's regression test and adjustments based on Duval and Tweedie's trim and

Study names	Odds ratio	Stat Lower limit	istics for e Upper limit	ach study Z-Value	P-Value	EUS-GE	SGJ		Odds Ratio ar	nd 95% CI	Relative weight
Khashab et al.	0.048	0.002	0.919	-2.016	0.044	26/30	63/63	4			18.79
Perez-Miranda et al.	0.109	0.005	2.218	-1.442	0.149	22/25	29/29	<pre>\u00e4</pre>		_	18.12
Widmer et al.	0.709	0.013	37.986	-0.169	0.866	10/10	14/14	_			10.39
Marya et al.	0.479	0.025	9.090	-0.490	0.624	168/172	39/39				18.99
Bondi et al.	0.160	0.006	4.048	-1.112	0.266	17/18	34/34	$\leftarrow$			15.75
Kouanda et al.	0.331	0.016	6.838	-0.715	0.474	33/36	14/14	-			17.96
	0.195	0.054	0.702	-2.500	0.012						
								0.01	0.1 1	10	100
									Favours SGJ	Favours EUS-GE	

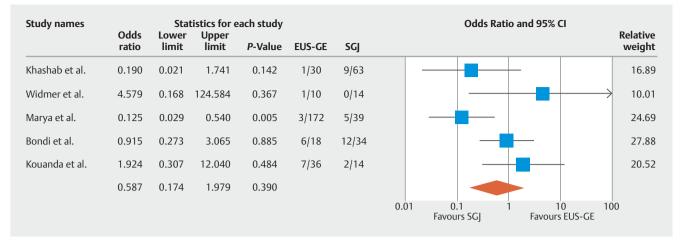
▶ Fig. 3 Forest plot for EUS-GE vs SGJ technical success. Pooled OR = 0.195 (95%CI:0.054-.702). Prediction interval = 0.032 to 1.197 [The true effect size (OR) in 95% of all populations falls in this interval]



▶ Fig. 4 Forest plot for EUS-GE vs SGJ clinical success. Pooled OR = 1.566 (95%CI: 0.584–4.197). Prediction Interval = 0.108 to 22.685 [The true effect size (OR) in 95% of all populations falls in this interval]

Study names	Statistics for each study Odds Lower Upper						Odds Ratio and 95% CI			Relative
	ratio	Lower limit	Upper limit	P-Value	EUS-GE	SGJ				weight
Khashab et al.	0.571	0.185	1.770	0.332	5/30	16/63			<b> </b>	22.85
Perez-Miranda et al.	0.196	0.048	0.808	0.024	3/25	12/29			-	14.58
Widmer et al.	0.111	0.005	2.330	0.157	0/10	4/14	<u> </u>		<u> </u>	3.15
Marya et al.	0.226	0.077	0.667	0.007	8/172	7/39				24.98
Bondi et al.	0.359	0.097	1.323	0.124	4/18	15/34		<b></b>	+	17.15
Kouanda et al.	0.250	0.068	0.919	0.037	9/36	8/14			_	17.29
	0.295	0.172	0.506	0.000				•		
							0.01	0.1 Favours SGJ	1 10 Favours EUS-	100 GE

**Fig.5** Forest plot for EUS-GE vs SGJ adverse events. Pooled OR = 0.295 (95%CI: 0.172–0.506). Prediction interval = 0.137–0.634 [The true effect size (OR) in 95% of all populations falls in this interval].



<sup>▶</sup> Fig.6 Forest plot for EUS-GE vs SGJ recurrence/reintervention rates. Pooled OR=0.587 (95%CI:0.174–1.979). Prediction interval=0.022 to 15.360 [The true effect size (OR) in 95% of all populations falls in this interval].

fill technique were also performed [28, 29]. Analysis using these techniques did not show evidence of significant publication bias. (Supplemental Fig.5, Supplement Fig.6, Supplement Fig.7). Sensitivity analysis for each outcome by removing one study at a time was done and the results are shown in Supplemental Fig.1, Supplemental Fig.2, Supplemental Fig.3, and Supplemental Fig.4.

# Discussion

Malignancy is the most common cause of GOO [30]. Malignant GOO carries an overall poor prognosis in patients who cannot be offered surgical cure and for these patients with unresectable disease, the management of GOO involves reducing their symptom burden, improving nutritional status, and improving the patient's quality of life [31]. Choosing an appropriate treatment needs to factor in the patient's medical co-morbidities, expected prognosis, and chances of technical success. Palliative care in terminal patients with malignant GOO should ideally be as least invasive as possible, provide long-term symptom relief, cause the least morbidity, and improve quality of life. Additionally, interventions should not prolong length of hospitalization and allow for palliative chemotherapy without complications or delay in recovery. With the available endoscopic procedures, surgery is reserved for patients deemed surgical candidates and with an expected prognosis that can justify the surgical risk [4]. With higher rate of AEs and morbidity associated with surgery, a less invasive endoscopic procedure that can offer comparable outcomes with less complications would be an ideal option. EUS-GE may be able to provide a more ideal intervention in this patient population, but supporting data is dearth. This led us to perform this systematic review and meta-analysis of the available literature and data on this subject.

Our study showed that technical success rates of EUS-GE were inferior to SGJ (OR=0.195; 95%CI: 0.054–0.702; P= 0.012). However, clinical success rates were comparable between EUS-GE and SGJ with odds ratio favoring EUS-GE, how-

ever this did not achieve statistical significance (OR=1.566; 95%CI: 0.585–4.197; *P*=0.372). Lower technical success of EUS-GE compared to SGJ could be due to several reasons: EUS-GE is a new and technically challenging procedure which needs significant expertise. Its rate of technical success may improve with more experience and utilization. The EUS-GE procedure is not standardized and five different techniques to achieve EUS-GE have been described [9]. Involvement of malignant GOO in the small bowel, especially in the region of the ligament of Treitz, can render the procedure technically challenging and even prove impossible as this small bowel section is typically adjacent to stomach [16]. Being a newer, non-standardized procedure, the studies involved may have reflected the early experience in the technique and the learning curve effect may have contributed to lower technical success as well.

The adverse event rates of EUS-GE were significantly lower compared to SGI (OR=0.295; 95%CI: 0.172-0.506; P<0.005). Also, among the five studies that reported recurrence and/or reintervention rates, there was no statistically significant difference between these two groups [15-17, 19, 20]. Therefore, if technically feasible, EUS-GE can provide long-lasting clinical success encompassing symptom improvement and diet tolerance while also posing lower adverse event rates compared to SG| in patients with malignant GOO. Two studies performed cost analysis on procedural costs between EUS-GE versus SG [17, 18]. As per the study by Perez-Miranda et al, the procedural costs were calculated to be \$4,515 for EUS-GE vs \$14,778 for SGJ (P<0.001) [18]. Similarly, in the study by Kouanda et al, the procedural costs were \$19,785 vs \$42,716, respectively (P <0.001) [17]. Differences in calculated costs are likely due to different techniques used as one study used Medicare reimbursement rates while the other used charge rate billed to payor. Nevertheless, in both studies EUS-GE is associated with significantly lower costs than SGJ.

A recent systematic review and pooled analysis by Duarte-Chavez et al. showed results similar to our analysis [32]. Clinical success rates were similar in both groups while EUS-GE was associated with lower rates of AEs and higher rates of technical success than SGJ. This study conducted a pooled analysis of three studies comparing EUS-GE vs enteral stenting and two studies comparing EUS-GE vs SGJ. However, in our study, we only included studies that directly compared EUS-GE vs SGJ head-to-head. While all the studies included in our analysis involved patients with malignant GOO, three studies also included patients with benign etiologies. The analysis was done only among patients with malignant GOO in four studies [15–17, 19]. However, in the remaining two studies by Perez-Miranda et al and Marya et al [18, 20], our analysis included patients with benign GOO as well, nevertheless, the majority of patients were with malignant GOO which comprised of 85% and 76.3% of their study populations respectively.

Our study has several strengths. To our knowledge, this is the first systematic review and meta-analysis involving all studies directly comparing EUS-GE vs SGJ. Studies were identified after a rigorous, comprehensive, and systematic search across multiple databases and conference proceedings. A well-defined inclusion and exclusion criteria were used with a detailed guality assessment. Heterogeneity in the analysis of technical success and AEs were low. Half of the included studies were international multicenter studies. There are some limitations to our study. All the involved studies were retrospective comparative studies with inherent limitations and risk of bias. The Studies have tried to limit selection bias by selecting all the patients within a certain time period, however, without randomization, selection of a procedure in a particular patient might have been biased due to various confounders. It is possible that a sicker patient might have been assigned to receive a lesser invasive procedure, affecting the outcomes. Three studies involved in the analysis were reported only as abstracts with limited details regarding them; however, the outcomes of interests pertaining to our study were clearly reported [15, 19, 20]. Also, the abstract by Marya et al. contributes to >50% of the total EUS-GE patients involved in this study, however, the weight assigned to the study in the random effects model used in the meta-analysis was only approximately 19% to 24%. In addition, all the studies were conducted at tertiary referral centers with significant expertise in therapeutic EUS, therefore the results cannot be generalizable. Heterogeneity in the assessment of clinical success and recurrence/reintervention rates were high which can be attributed to multiple factors, such as the low number of studies included and small number of patients in each study. Three studies were multicenter studies in which EUS-GE was performed by different operators internationally, which limits the standardization of techniques, given there are multiple techniques for EUS-GE [9, 18]. While some studies only used electrocautery-enhanced LAMS, some studies incorporated procedures performed both with or without electrocautery-enhanced LAMS, which could have impacted the outcomes. Finally, SGJ is an older and more refined procedure compared to the novel EUS-GE, which is evolving. Most of the SGJ procedures in the cohort likely were done in a prior time period, whereas EUS-GE was done in recent years. Hence, we can safely assume the cohorts were not entirely contemporaneous. Furthermore, some studies used an open approach to SGJ while others used laparoscopic GI or both and our study lacks a direct comparison

between EUS-GE and the current standard of care, laparoscopic GJ. Three studies reported only patients with open GJ and two abstracts did not specify the nature of surgery. Limited studies with information on laparoscopic GJ also did not allow us to perform a subgroup analysis comparing EUS-GE vs laparoscopic GJ.

# Conclusions

Advances in endoscopic procedures have allowed for a paradigm shift in the approach and treatment of patients with malignant GOO where the primary goal is symptom palliation. While enteral stents were initially more commonly used than SGJ in this patient population, symptom recurrence and reintervention was a major disadvantage. Through the advent of LAMS, the ability to perform minimally invasive intraluminal gastroenterostomy has led to the development of EUS-GE, which has the potential to help treat this sick patient population and achieve long-lasting symptom relief and palliation. This study shows that EUS-GE is similar to SGJ in delivering clinical success and avoiding reinterventions, and better than SGJ in terms of AEs rates even in the initial learning curve period in specialized centers. EUS-GE is rapidly evolving and with further expertise and experience we anticipate the technical success rates to improve as well.

When expertise is available, EUS-GE is an effective and safe alternative to SGJ in the treatment of malignant GOO, for which data are available on long-term outcomes. Larger prospective randomized studies are required to validate our results.

#### **Competing interests**

The authors declare that they have no conflict of interest.

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