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Reconstruction Techniques and Associated Morbidity in Minimally Invasive Gastrectomy for Cancer – Insights from the GastroBenchmark and GASTRODATA databases

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Han-Kwang Yang, Christian Alexander Gutschow	Conception and design of this study, analysis and interpretation of all data, drafting and revision and final approval of the manuscript.

Structured Abstract

Objective/Background:

Various anastomotic and reconstruction techniques are used for minimally invasive total (miTG) and distal gastrectomy (miDG). Their effects on postoperative morbidity have not been extensively studied.

Methods:

MiTG and miDG patients were selected from 9356 oncological gastrectomies performed 2017-2021 in 44 centers. Endpoints included anastomotic leakage (AL) rate and postoperative morbidity tested by multivariable analysis.

Results:

Three major anastomotic techniques (circular stapled (CS); linear stapled (LS); hand sewn (HS)), and three major bowel reconstruction types (Roux (RX); Billroth I (BI); Billroth II (BII)) were identified in miTG (n=878) and miDG (n=3334). Postoperative complications including AL (5.2% vs. 1.1%), overall (28.7% vs. 16.3%) and major morbidity (15.7% vs. 8.2%), as well as 90-day mortality (1.6% vs. 0.5%) were higher after miTG compared with miDG.

After miTG, AL rate was higher after CS (4.3%) and HS (7.9%) compared with LS (3.4%). Similarly, major complications (LS: 9.7%, CS: 16.2%, HS: 12.7%) were lowest after LS. Multivariate analysis confirmed anastomotic technique as predictive factor for AL, overall and major complications.

In miDG, AL rate (BI: 1.4%, BII 0.8%, RX 1.2%), overall (BI: 14.5%, BII: 15.0%, RX: 18.7%,) and major morbidity (BI: 7.9%, BII: 9.1%, RX: 7.2%), and mortality (BI: 0%, BII: 0.1%, RY: 1.1%%) were not affected by bowel reconstruction.

Conclusion:

In oncologically suitable situations, miDG should be preferred to miTG, as postoperative morbidity is significantly lower. LS should be a preferred anastomotic technique for miTG in Western Centers. Conversely, bowel reconstruction in DG may be chosen according to surgeon's preference.

Introduction

Minimally invasive gastrectomy (miG) is now being increasingly recommended by national and international guidelines as a standard approach for gastric cancer[1-5]. For early-stage tumors, guidelines are unanimously favoring minimally invasive distal gastrectomy (miDG), but are inconsistent regarding minimally invasive total gastrectomy (miTG), as long-term oncological results are still pending. For advanced gastric cancer, recommendations are mixed and European guidelines still advocate open access surgery because of the lack of long-term evidence[6]. Nevertheless, the body of scientific work demonstrating miG as a non-inferior option for both early and advanced stage gastric cancer is growing rapidly and includes several recent randomized controlled trials[7-15] and meta-analyses[16-20]. Consequently, MiG has rapidly gained popularity and became the surgical standard for gastric cancer in many centers. It is expected that guidelines will be updated soon.

With the introduction of miG, many new technical details have emerged, which either are modifications of open techniques or have been adopted from established minimally invasive procedures, such as gastric bypass surgery for obesity. However, no reliable information exists about the manifold technical variations in miG regarding anastomotic technique and intestinal reconstruction methods and how these technical variations may influence postoperative morbidity. Meta-analyses for open gastrectomy show that different reconstruction techniques are equally safe[21, 22], and consequently, no consensus about optimal anastomotic techniques or reconstruction methods has been established yet[1, 23]. In addition, Asian centers have developed advanced function-preserving partial gastrectomy for early-stage cancer[24-26]. The current state of the art in miG is therefore not only characterized by a heterogeneity of anastomotic techniques and bowel reconstructions, but also of resection types (proximal, distal, pylorus-preserving, and total gastrectomy). In this context, current discussions show that even specialized upper GI surgeons do not conclude on uniform techniques[21, 23, 27].

Against this background, the aim of this global multicenter study was to analyze short-term morbidity associated with different anastomotic and bowel reconstruction techniques for miG. To streamline our research, we focused on miTG and miDG, as these procedures represent globally accepted standards for both early and advanced gastric cancer.

Methods

Study Design & Data Collection

We performed a multicentric retrospective analysis of consecutive patients ≥18 years undergoing elective miG for adenocarcinoma between 01.01.2017 and 31.12.2021. Data was collected as part of the international GastroBenchmark[28] and European GASTRODATA[29, 30] collaboratives. Center inclusion criteria were an average annual caseload of ≥20 oncological gastrectomies and maintaining a prospective database. Approval from the ethical committees of Zurich, Switzerland (BASEC-No. 2022-00931) and each participating center was obtained before patient inclusion.

De-identified patient-specific data omitting any patient or hospital identifiers was transmitted securely and audited for integrity and completeness. The information collected encompassed basic demographics and information on comorbidities, tumor-related parameters, technical details of the surgical procedure, and a comprehensive assessment of postoperative complications, which were assessed up to postoperative day 90. Complications were categorized as performed at the Seoul National University Hospital, South Korea,[11, 12] and the GASTRODATA collaborative (European Chapter of the International Gastric Cancer Association)[29], and graded according to the Clavien-Dindo (CD) classification[31]. Cumulative morbidity was assessed with the Comprehensive Complication Index (CCI®)[32].

Study Cohort and Inclusion Criteria

MiG was defined as a laparoscopically or robotically assisted gastrectomy including a mini-laparotomy <8cm for specimen retrieval. All reconstruction and anastomotic techniques were incorporated in the current analysis except 11 cases with missing data on reconstruction, while conversions to open surgery were excluded.

Endpoints

Outcomes were postoperative complication rates and their respective associations with anastomotic and intestinal reconstructions techniques after miTG and miDG. Primary endpoint was overall and major (defined as re-intervention under general anesthesia, CD≥IIIB) anastomotic leakage (AL), while secondary endpoints included overall and major (CD≥IIIA) morbidity, cumulative morbidity as measured by the CCI®, 90-day mortality and the rate of specific complications including pulmonary problems, hemorrhages, infections, ileus and strictures. The composite endpoint "infection" included rates of superficial and deep surgical site infections, abdominal fluid collections and unspecified infections.

Statistical Analysis

Categorical variables are presented as number (n) or percentage (%) and were compared with Fisher's exact test, while numeric variables are expressed as median ± interquartile range (IQR) and compared by Wilcoxon's rank sum test. Association of variables to binary outcomes (e.g. AL) were examined by generalized multivariable linear mixed-effects model with centers included as random effect reporting odds ratios (OR) with respective 95% confidence intervals (CI). Statistical significance was defined as $p < 0.05$. *R* V4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses and figures.

Results

Basic Patient Characteristics and Procedure-Specific Outcomes

From a cohort of 9356 oncological gastrectomies, performed at 43 tertiary centers from 5 continents (Europe, Asia, North & South America, Africa, Appendix 1, Supplemental Digital Content 1, http://links.lww.com/SLA/F236), 4212 patients from 36 centers undergoing miTG (n=878) and miDG (n=3334) for gastric adenocarcinoma were identified. Patients of the study cohort were predominantly male (63.3%) with a median age of 65 years (IQR 56-73). 71.1% were operated at East Asian centers and most patients had low comorbidity with an ASA score of 1-2 (78.9%). Most tumors were located in the antrum and corpus and only a minority received induction chemotherapy before surgery. R0-resection was achieved in 98.5% of patients.

Comparing miTG and miDG patients, age and gender ratio were similar, but miDG cases had lower BMI, less comorbidity, earlier tumor stages, and were more likely operated at East Asian centers. Overall and procedure-specific basic characteristics are detailed in Supp. Table 1, Supplemental Digital Content 1, http://links.lww.com/SLA/F236. Postoperative morbidity was consistently higher after miTG compared to miDG including overall and major morbidity, CCI®, AL rate, pulmonary & infectious complications except for postoperative hemorrhage and ileus. Overall and procedure-specific outcomes are detailed in Table 1.

Anastomotic Techniques

Three main techniques were identified in the whole cohort: linear stapling (62.3%), circular stapling (22.6%) and hand sewn (2.2%).

In miTG cases (LS 23.5%, CS 47.9%, HS 7.2%), AL and major complication rates as well as infectious complications were higher after CS and HS than in LS anastomoses. In contrast, overall morbidity, CCI®, pulmonary complications, hemorrhage and mortality were similar among anastomotic techniques (Table 2). Multivariate analysis identified anastomotic technique as a predictive factor for overall (Fig 1A) and major AL, overall, major (Fig 1B) and infectious complications, but not for other complications.

In miDG cases, LS anastomosis was performed in 72.5% of patients (mainly Billroth II (BII)), while CS was done in 16% (all Billroth I (BI)) and HS in 0.9%. Similar to miTG, overall and major AL as well as overall and major complications were lowest after LS (Table 2) and proved predictive in multivariable analysis (Supp Fig. 1, Supplemental Digital Content 1, http://links.lww.com/SLA/F236). CCI®, mortality and pulmonary complications were similar in LS and CS but markedly increased in the few reported HS. Other specific complications were not different among techniques (Table 2).

Subgroup Analysis: East Asia vs. Europe/America in miTG

Undergoing miG at East Asian (n=429) compared to European/American centers (n=449) was a predictive factor for lower AL, and overall and major morbidity in multivariate analysis.

Consequently, we performed separate subgroup analyses for both world regions, showing higher AL rates, overall, major, and infectious complications after CS compared to LS in Europe/America (Supp. Table 2, Supplemental Digital Content 1, http://links.lww.com/SLA/F236). Anastomotic technique remained a significant predictive factor for these outcomes in multivariate analysis. In contrast, mortality, pulmonary complications, and hemorrhage were not affected by anastomotic technique in Western centers. In contrast, in Asian patients, AL (CS:1.8%, LS: 1.1%) and all other outcomes were similar after CS and LS (Supp. Table 2, Supplemental Digital Content 1, http://links.lww.com/SLA/F236). Anastomotic techniques were not predictive for AL, complications, or mortality in East Asia, except for infectious complications, which were more frequent after CS compared to LS in both world regions. As previously described[28], the incidence of pulmonary complications was higher in European/American compared to East Asian patients; however, without clear association to anastomotic techniques in both cohorts.

Intestinal Reconstruction Techniques

In the miTG cohort, all patients underwent Roux (RX) reconstruction, precluding subgroup-specific analysis. In miDG, intestinal reconstruction was performed with BI, BII, and RX in 29.1%, 32.1%, and 38.8%, respectively (Table 3). Reconstruction techniques were not associated with AL (Fig 2A), major complications (Fig. 2B) or the CCI®. While incidences of overall complications, mortality, pulmonary and hemorrhage showed certain baseline differences (Table 3), intestinal reconstruction was not associated with any of these outcomes in multivariable analysis.

Subgroup Analysis: East Asia vs. Europe/America in miDG

Separate analysis of East Asian (n=2591) and European/American miDG patients (n=743) revealed that BI and BII were the most popular techniques in Asia (BI: 37.3%, BII: 39.5%, RX: 23.2%), while RX was the preferred reconstruction method in Europe (BI: 0.7%, BII: 6.2%, RX: 93.1%).

In Asian patients, reconstruction method did not influence AL rate, overall complications, pulmonary problems, hemorrhage, or infectious complications; however, major complications (BI: 7.8%, BII: 8.8%, RX: 3.5%, p=0.007) and CCI® were lower after RX compared with Billroth reconstructions (Supp. Table 3, Supplemental Digital Content 1, http://links.lww.com/SLA/F236). In European/American patients, statistical comparison was limited owing to the low number of non-RX cases. However, a higher complication rate was found in BI patients (Supp. Table 3, Supplemental Digital Content 1, http://links.lww.com/SLA/F236).

Discussion

This large international multicenter study comprehensively analyzes anastomotic and intestinal reconstruction techniques in miG performed at expert centers. A first observation was that surgical morbidity was significantly lower in miDG compared with miTG. This result was expected, as it confirms previous research findings[33-35] and supports the recommendation that distal gastrectomy should be the preferred surgical option in oncologically suitable situations[36] because of lower early postoperative morbidity and better long-term quality of life[37-40]. This might be especially relevant in Europe, where

guidelines still recommend a proximal safety margin of 5 (ESMO[2]) - 8cm (German S3[1]) in diffuse gastric cancer based on data from 1990[41]. Among other factors, this - probably outdated - recommendation could explain the higher proportion of TG performed in Western centers (37.7%) compared to East Asia (14.2%). Large-scale studies in advanced gastric cancer have shown that R1 resection can be reliably avoided by a ≥3cm macroscopic proximal margin and negative intraoperative frozen section - even in diffuse type gastric cancer[42]. We believe that these findings should be implemented in the next guideline versions, as this will likely lead to a higher proportion of patients undergoing DG, thereby avoiding unnecessary morbidity.
Another finding of this study is that all miTG patients in this study had RX reconstruction. We believe that this mirrors the technical requirements of total gastrectomy, as RX provides better protection from reflux of duodenal secretions to the esophagus[21-23] and allows for easier creation of a tension-free anastomosis compared to e.g. jejunal interposition. In contrast, intestinal reconstruction was quite variable in miDG, reflecting current guideline statements that surgeons may take case-specific decisions owing to the lack of impact on functional outcomes[1, 3, 43]. This recommendation is supported by our current analysis, which showed no impact on postoperative morbidity in different types of bowel reconstruction.
Anastomotic techniques were very uniform in miDG for RX (94.4% LS) and BII (99.9% LS) reconstruction, reflecting the advantages of LS, as it is technically straightforward and allows intracorporeal creation of large anastomoses through standard 10-12 mm trocars. LS is therefore popular not only in minimally invasive oncologic but also in bariatric surgery[45]. In addition, LS has a low leakage rate in miDG and is easier and faster to perform than HS side-to-side anastomosis, which can be challenging to perform laparoscopically even in experienced hands[44]. However, with the increasing popularity of the robot-assisted technique, which enables simple and safe hand-sewn anastomoses, HS will be performed more frequently.
In BI reconstruction, which is rarely performed in Western centers, LS and CS were performed equally frequently (47.7 % vs. 52.3 %) and had no influence on the AL rate (0.9 vs. 2.0 %, p= 0.1945).
In contrast, anastomotic technique was very variable in the miTG group. We believe that this finding mainly highlights the technical challenges of minimally invasive esophago-jejunostomy in general. CS, which is traditionally a very popular option in all types of end-to-side gastrointestinal anastomoses, was the most used technique. Nevertheless, AL, overall and major complication rates were lowest after LS. While previous research identified comorbidities and MIS as predictive factors for AL[46], our multivariate analysis

found anastomotic technique as prognostic for AL besides being operated at an East Asian center. Nevertheless, one must consider that the esophageal stapler donut, which is excised during CS, provides additional oncologic safety due to a wider proximal tissue margin, which can be a crucial factor in higher located gastric tumors. Therefore, our results may be biased by oncologic issues such as tumor location and we believe that the anastomotic technique for miTG should be carefully selected on a case-by-case basis.

Limitations of our study include the inherent heterogeneity of retrospective data collections. Specifically, patients from East Asia showed markedly different demographic and tumor characteristics compared with their Western counterparts. To account for these known differences, we performed subgroup-specific analyses, which showed that the better results of LS compared to CS were only present in Western centers, while no relevant difference between the anastomosis techniques was seen in the high volume East Asian centers of our study. A possible recommendation in favor of LS in miTG can therefore only be made for Europe/America.

Furthermore, we were not able to sub-differentiate technical anastomotic details. Thus, a LS side-to-side anastomosis can be performed with the classical "overlap" technique, but also in an an-isoperistaltic functional end-to-end fashion or as a π-shaped anastomosis[44]. Likewise, our dataset did neither allow identification of different HS techniques, oversewing of anastomoses, nor the creation of CS or LS subgroups, which can be performed with different stapler sizes. Furthermore, we did not have the data to identify different options for securing the stapler anvil in CS, such as sewn purse-string sutures, double-stapling (Orvil®), or the reverse puncture technique[47].

A strength of our study is the international multi-center design including a large cohort of miG and involving only high-volume institutions with abundant experience in oncological gastric surgery. However, it is noteworthy that there was a substantial variability in case numbers per center. Thus, caseloads from East Asian centers were considerably higher compared with European and American institutions. While this variability may be considered a strength better reflecting reality than a single high-volume experience, it may also indicate that differences in experience with a specific procedure and learning curve-related morbidity can have an impact on the results. Based on these considerations, the conclusions of this retrospective analysis may be limited, as anastomotic leakage rate may not only reflect the quality of the technique itself but may also be a surrogate of surgical experience even in expert centers[48-50].

In conclusion, AL was the predominant surgical complication and multivariate analysis identified anastomotic techniques as an independent factor of leakage. Furthermore, our results support the following recommendations: a) if oncologically feasible, miDG should be preferred to miTG as postoperative morbidity is significantly lower, b) in Western centers, LS should be a preferred option for miTG due to low AL and complication rates, and c) intestinal reconstruction in miDG may be chosen according to surgeon's preference and oncological requirements. Nevertheless, it is important to note that results of this analysis present the current status of an ongoing technical evolution and therefore must be cautiously interpreted in consideration of the learning curve of miG. Structured training curricula are desirable to accelerate the learning process of this complex surgical procedure.

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Figure 1

(A) OR plot of multivariable logistic regression model assessing the influence of anastomotic technique and other variables on anastomotic leakage after minimally invasive total gastrectomy. (B) OR plot of multivariable logistic regression model assessing the influence of anastomotic technique and other variables on major complications after minimally invasive total gastrectomy.

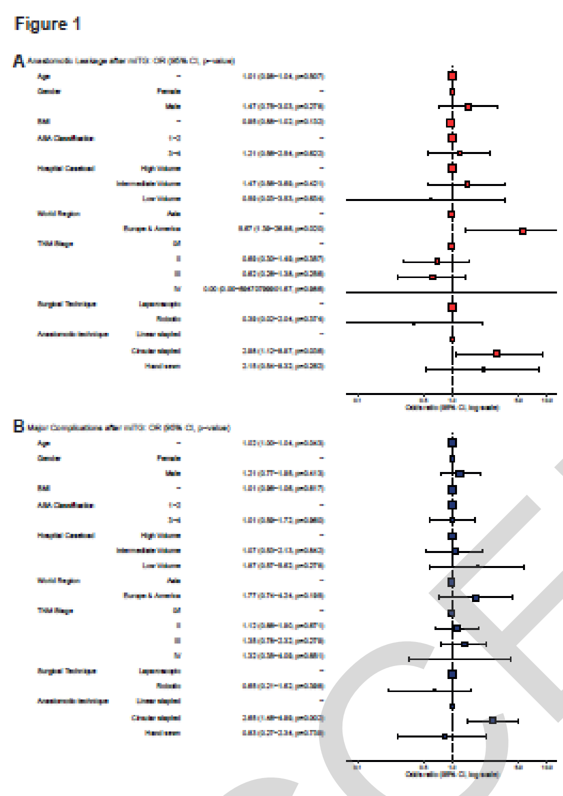

Figure 2

(A) OR plot of multivariable logistic regression model assessing the influence of intestinal reconstruction technique and other variables on anastomotic leakage after minimally invasive distal gastrectomy. (B) OR plot of multivariable logistic regression model assessing the influence of intestinal reconstruction technique and other variables on major complications after minimally invasive distal gastrectomy.

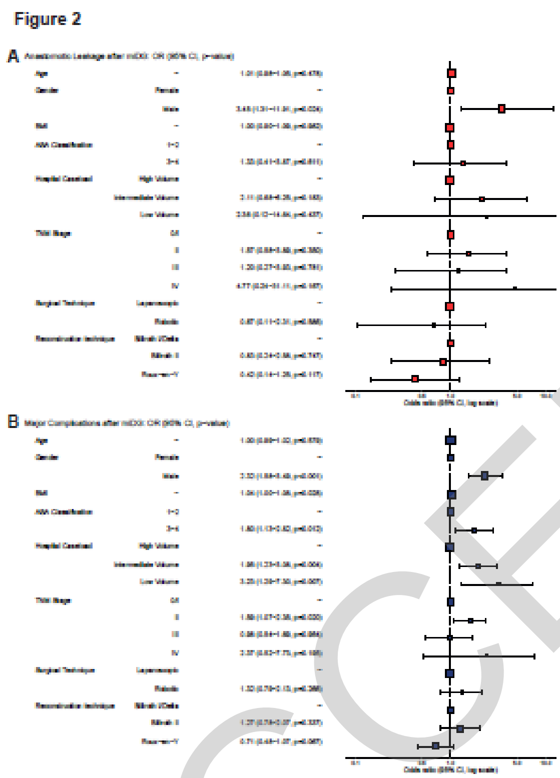

Table 1: Postoperative morbidity & outcomes of the cohort, stratified by type of gastrectomy

	miTG (n=878)	**miDG (n=3334)**	**p-value**	**Total (n=4212)**
Overall complication rate				
None	71.3%	83.7%	<0.001	81.1%
Minor (CD I-II)	13.0%	8.1%		9.1%
Major (CDIIIA-V)	15.7%	8.2%		9.7%
Specific complications				
Anastomotic Leakage	5.2%	1.1%	<0.001	2.0%
Minor (CD I-IIIA)	2.5%	0.6%	<0.001	1.0%
Major (CDIIIB-V)	2.7%	0.5%		1.0%
Pulmonary complications	7.1%	2.3%	<0.001	3.3%
Hemorrhage	1.6%	1.6%	1	1.6%
Infectious Complications	6.8%	4.1%	0.002	4.7%
Ileus	1.8%	1.8%	1	1.8%
Strictures/Stenosis	1.1%	1.7%	0.231	1.6%
CCI® (Median [IQR])	26.2 (20.9-33.7)	26.2 (20.9-33.5)	<0.001	26.2 (20.9-33.7)
Escalation of care	4.7%	2.0%	<0.001	2.6%
Reoperation	5.9%	1.7%	<0.001	2.6%
Hospital stay (Days, Median [IQR])	10 [9, 14]	10 [9, 11]	<0.001	10 [9, 12]
Readmission related to Gastrectomy	4.2%	1.7%	0.007	2.3%
Mortality				
30-Day	1.4%	0.3%	<0.001	0.5%
90-Day	1.6%	0.5%	<0.001	0.7%

Table legend miTG: minimally invasive total gastrectomy; miDG: minimally invasive distal gastrectomy; IQR: interquartile range; CD: Clavien-Dindo, CCI®: comprehensive complication index

Table 2: Postoperative outcomes in relation to anastomotic techniques, stratified by type of gastrectomy

	miTG (n=878)				**miDG (n=3334)**			
Anastomotic technique (n, %)	**LS (n=206, 23.5 %)**	**CS (n=421, 47.9%)**	**HS (n=63, 7.2%)**	**p-Value**	**LS (n=2417, 72.5 %)**	**CS (n=532, 16%)**	**HS (n=31, 0.9%)**	**p-Value**
Anastomotic Leakage								
Total	3.4%	4.3%	7.9%	0.036	0.7%	2.4%	3.2%	0.003
Minor (CD I-IIIA)	2.4%	2.6%	1.6%	0.025	0.3%	1.7%	0%	0.002
Major (CD IIIB-V)	1.0%	1.7%	6.3%		0.4%	0.8%	3.2%	
Overall Complications	25.7 %	27.1%	28.6%	0.119	15.8 %	18.0%	22.6%	0.452
Major (≥IIIA) Complications	9.7%	16.2%	12.7%	0.014	7.0%	12.2%	12.9%	≤0.001
CCI® (Median [Q1, Q3])*****	20.9 (20.9-33.7)	26.2 (20.9-33.5)	24.4 (20.9-32.67)	0.856	20.9 (20.9-29.6)	26.2 (20.9-26.2)	39.7 (28.15-100)	≤0.001
30-Day Mortality	1.5%	1.2%	0%	0.616	0.1%	0.4%	9.7%	≤0.001
90-Day Mortality	1.9%	1.2%	0%	0.394	0.3%	0.4%	9.7%	≤0.001
Pulmonary Complications	8.3%	4.8%	6.3%	0.424	2.3%	1.1%	6.5%	0.035
Hemorrhage	0%	1.7%	3.2%	0.126	1.6%	0.8%	0%	0.091
Infectious Complications	3.9%	10.2%	4.8%	0.002	4.1%	4.3%	0%	0.676
Ileus	1.0%	2.4%	1.6%	0.690	1.6%	1.9%	6.5%	0.127
Strictures/Stenosis	1.0%	1.9%	0%	0.205	1.1%	5.6%	0%	≤0.001

	miTG (n=878)				miDG (n=3334)			
Anastomotic technique (n, %)	**LS (n=206, 23.5%)**	**CS (n=421, 47.9%)**	**HS (n=63, 7.2%)**	**p-Value**	**LS (n=2417, 72.5%)**	**CS (n=532, 16%)**	**HS (n=31, 0.9%)**	**p-Value**

Table legend miTG: minimally invasive total gastrectomy; miDG: minimally invasive distal gastrectomy; LS: linear stapling, CS: circular stapling, HS: hand sewn; IQR: interquartile range; CD: Clavien-Dindo, CCI®: comprehensive complication index.
***calculated in patients with occurrence of complications only.

Table 3: Postoperative outcomes in relation to intestinal reconstruction, stratified by type of gastrectomy

	miTG (n=878)	**miDG (n=3334)**			
Intestinal reconstruction technique (%)	**RX (n=2981, 100%)**	**BI (n=971, 29.1%)**	**BII (n=1070, 32.1%)**	**RX (n=1293, 38.8%)**	**p-Value**
Anastomotic Leakage					
Total	5.2%	1.4%	0.8%	1.2%	0.441
Minor (CD I-IIIA)	2.5%	1.1%	0.5%	0.3%	0.146
Major (CD IIIB-V)	2.7%	0.3%	0.3%	0.9%	
Overall Complications	28.7%	14.5%	15.0%	18.7%	0.011
Major (≥IIIA) Complications	15.5%	7.9%	9.1%	7.2%	0.247
CCI® (Median [Q1, Q3])*	26.2 (20.9-33.7)	26.2 (20.9-26.2)	26.2 (20.9-33.5)	26.2 (20.9-33.7)	0.150
30-Day Mortality	1.4%	0%	0.1%	0.8%	0.001
90-Day Mortality	1.6%	0%	0.1%	1.1%	≤0.001
Pulmonary Complications	7.1%	1.1%	2.2%	3.2%	0.003
Hemorrhage	1.6%	0.7%	1.4%	2.3%	0.008
Infectious Complications	6.8%	4.2%	4.0%	4.2%	0.970
Ileus	1.8%	1.9%	1.8%	1.8%	0.988
Strictures/Stenosis	1.1%	3.3%	2.1%	0.2%	≤0.001

Table legend miTG: minimally invasive total gastrectomy; miDG: minimally invasive distal gastrectomy; RX: Roux-en-Y, BI: Billroth I, BII: Billroth II; IQR: interquartile range; CD: Clavien-Dindo, CCI®: comprehensive complication index. *****calculated in patients with occurrence of complications only.

#19

ANNSURG-D-24-00428	**Christian A. Gutschow**	**Reconstruction Techniques and Associated Morbidity in Minimally Invasive Gastrectomy for Cancer – Insights from the GastroBenchmark and GASTRODATA databases**	**ESA Paper**

First Discussant: Raul Rosenthal (Weston, Florida, United States)

Thank you for the nomination to ESA and the opportunity to comment on this paper. Congratulations, Dr. Schneider and the rest of the team, for a wonderful presentation. Around 25 years ago, I remember Prof. Hans Troidl, the Chief of Surgery in Cologne, Germany, debating an Asian surgeon and saying that he thinks they're operating on different diseases because the Asian-Pacific region usually has the distal intestinal type of cancer, which is less aggressive, while what we see in the western world is mainly the proximal poorly differentiated type that has worse prognosis. So, that's probably why the outcomes are different.

However, this is an outstanding work. It's a huge database, which we can all benefit from. The patient cohort seems to be too diverse to draw conclusions. There are significant variations in patient demographics (age, BMI, ASA), tumor type (Adeno vs. Poorly dif.) tumor location (proximal vs. distal), and surgical techniques (BII vs. Roux-en-Y). I have the following comments and questions:

First, despite leaks being the primary endpoint of the analysis, it is unclear how they were identified and or defined.

Second, isn't it essential to have a clear understanding of the outcomes of anastomotic techniques, i.e., how limbs are routed to reconstruct the GI tract (ante-colic vs. retrocolic, division or not of mesentery); how, and if, staple lines have been reinforced (buttressing vs. oversewing)? These variables might result in bleeding, tension and/or ischemia affecting the outcomes of the analysis.

Finally, is there potential for improvement using new technology, such as Fluorescence Imaging with ICG and/or robotic assistance?

Response From Marcel A. Schneider (Zurich, Switzerland)

Thank you, Professor Rosenthal, for these very insightful comments and critical points raised. First, of course, the patient cohort suffers from a heterogeneity that is typical of a retrospective data collection of this size over several continents and multiple centers. This inherent patient heterogeneity needs to be addressed, but I think what you're mainly referring to is the Asian-Pacific hemisphere versus the Atlantic one, which consists of European and

American data. I agree that there are pronounced differences, as outlined in my talk, when it comes to age and tumor location between these world regions. According to our data, there actually isn't much difference when it comes to the type of gastric cancer, as Asian centers also have a lot of poorly differentiated cancers. In general, as long as these baseline differences are adequately addressed, I think that the heterogeneity is not an issue restricting the value of the analysis. This is why we performed a separate subgroup analysis for the Asian-Pacific and the Atlantic hemisphere. This subgroup analysis clearly shows that the differences between anastomotic techniques is caused by the European data, and we cannot really conclude anything for Asian patients, which make up a majority of our database. In summary, I believe that the heterogeneity is not a problem as long as it is adequately addressed and discussed in the manuscript.

To answer your first point, leaks were defined according to the European Gastrectomy Complications Database. This database provides clear definitions of post-operative complications after gastrectomy, which have been published in *Annals of Surgery*. The definition of anastomotic leakage is a full thickness defect of the wall of the intestinal tract, regardless of the method of diagnosis, the treatment and the clinical consequences. We included the reported rates of anastomotic leakages as they were recorded in the institutional databases. Additionally, we performed separate subgroup analyses on minor anastomotic leakages, i.e., the ones only treated with medical therapy or endoscopic treatments, compared to those who were re-operated (major anastomotic leakages). The overall findings regarding the influence of anastomotic techniques were also confirmed when we differentiated between minor and major anastomotic leakages, which made up around half of our database (half were minor and half were major).

Regarding your second point, there are many technical details that were not available in our database, which I would have loved to analyze further. It starts with the retro- vs. antecolic data that were not recorded. Also, we had no data on over-sewing of the anastomosis, which might very well influence the anastomotic leakage. We intended to further analyze stapler size (e.g., 45 versus 60mm linear stapling). Unfortunately, a lot of centers don't routinely include these data in their operation notes. This prevented us from doing meaningful subgroup analyses.

Regarding your last point, I think ICG imaging might reduce the rates of anastomotic leakages, and what we also see in our database is that we have very few hand-sewn anastomoses. I think they might be increasing with the uptake of robotics and could of course change the results of future analyses of anastomotic techniques.

Discussant: Thomas Schmidt (Cologne, Germany)

Congratulations on this big database and good data. I'm curious whether you're really comparing the same operation because, in many centers, we know that circular stapler anastomosis is usually used in esophagojejunostomy, whereas, for linear stapler anastomosis, many surgeons leave at least a rim of the stomach. We usually use a circular stapler when we need to perform a total gastrectomy with an esophagojejunostomy. I'm not sure you can really compare the anastomotic leak rate between these two techniques.

Response From Marcel A. Schneider (Zurich, Switzerland)

Thank you, Professor Schmidt, for this valuable comment. As mentioned in the conclusion of my talk, when you have to go very high up, circular stapling is normally the preferred choice. This is potentially an influencing factor and it's not something we can really account for in retrospective analyses. However, if you look at the data in our database, not that many centers performed linear stapling or circular stapling individually. Most centers stick to one technique, which they use routinely, regardless of patient- or surgery-specific factors, such as the exact location or height of the anastomosis.

Discussant: Stefan P. Mönig (Geneva, Switzerland)

Thank you for your discussion. I have one comment on the conclusion. From this data, I think that we cannot conclude that the linear stapler is a preferred technique. In the majority of the experienced centers that are doing esophageal and gastric cancer surgeries, the circular stapler technique is an excellent one. We know this from open, minimally invasive, and robotic surgery. It's probably the safest technique.

Response From Marcel A. Schneider (Zurich, Switzerland)

Thank you, Professor Mönig, for this clear statement. If you look at our conclusion, I clearly say that it should be a preferred technique, though not the only one. As I answered Professor Schmidt, there are certain situations where you need to opt for circular stapling. It definitively is a legitimate option, but I think that our large-scale data still show some clear differences between anastomotic techniques when it comes to various postoperative complications. There's also plenty of data available from other operations, such as gastric bypass, where outcomes with linear stapling are normally better, resulting in a lot of centers switching from linear to circular stapling. However, as I said, we should call it *a* preferred option rather than *the* preferred option.