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SYSTEMATIC REVIEWS AND META-ANALYSES

Techniques for reconstruction after distal gastrectomy for cancer: updated network meta-analysis of randomized controlled trials

Francesca Lombardo[1] · Alberto Aiolfi[1] · Marta Cavalli[1] · Emanuele Mini[1] · Caterina Lastraioli[1] · Valerio Panizzo[1] · Alessio Lanzaro[1] · Gianluca Bonitta[1] · Piergiorgio Danelli[2] · Giampiero Campanelli[1] · Davide Bona[1]

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Abstract

Background The choice of the best reconstruction technique after distal gastrectomy (DG) remains controversial and still not defined. The purpose was to perform a comprehensive evaluation within the major type of intestinal reconstruction after DG for gastric cancer.

Methods Systematic review and network meta-analyses of randomized controlled trials (RCTs) to compare Billroth I (BI), Billroth II (BII), Billroth II Braun (BII Braun), Roux-en-Y (RY), and Uncut Roux-en-Y (URY). Risk ratio (RR) and weighted mean difference (WMD) were used as pooled effect size measures while 95% credible intervals (CrI) were used to assess relative inference.

Results Ten RCTs (1456 patients) were included. Of these, 448 (33.7%) underwent BI, 220 (15.1%) BII, 114 BII Braun (7.8%), 533 (36.6%) RY, and 141 URY (9.6%). No significant differences were found among treatments for 30-day mortality, anastomotic leak, anastomotic stricture, and overall complications. At 12-month follow-up, RY was associated with a significantly reduced risk of remnant gastritis compared to BI (RR=0.56; 95% Crl 0.35–0.76) and BII reconstruction (RR=0.47; 95% Crl 0.22–0.97). Similarly, despite the lack of statistical significance, RY seems associated with a trend toward reduced endoscopically proven esophagitis compared to BI (RR=0.58; 95% Crl 0.24–1.51) and bile reflux compared to BI (RR=0.48; 95% Crl 0.17–1.41), BII (RR=0.74; 95% Crl 0.20–2.81), and BII Braun (RR=0.65; 95% Crl 0.30–1.43).

Conclusions This network meta-analysis shows that there are five main options for intestinal anastomosis after DG. All techniques seem equally safe with comparable anastomotic leak, anastomotic stricture, overall morbidity, and short-term outcomes. In the short-term follow-up (12 months), RY seems associated with a reduced risk of remnant gastritis and a trend toward a reduced risk of bile reflux and esophagitis.

Keywords Billroth I · Billroth II · Billroth II Braun · Roux-en-Y · Network meta-analysis

Introduction

Surgical resection with proper lymphadenectomy is the cornerstone for curable gastric cancer. The extent of gastrectomy depends on a comprehensive analysis of tumor location, size, histology, and surgeon experience. Distal gastrectomy (DG) with adequate resection margin is indicated for the treatment of gastric cancer located in the distal stomach.

The choice of the best reconstruction technique after DG remains controversial. Surgeons in the Asia-Pacific region favor the Billroth I (BI) and Billroth II (BII) while in Europe and in the USA surgeons tend to perform Roux-en-Y (RY) anastomosis [1, 2]. The RY reconstruction is technically challenging and alters the intestinal anatomy. On the contrary, BI and BII retain the intestinal continuity and are easier to perform; however, the chronic bile reflux into the stomach may cause remnant gastritis with a potential risk for gastric metaplasia [3, 4]. Previous pairwise meta-analyses [5–12] compared the type of reconstruction after DG. Kim et al. [7] reported that RY has some clinical advantages over

✉ Alberto Aiolfi
alberto.aiolfi86@gmail.com

[1] Department of Biomedical Science for Health, Division of General Surgery, University of Milan, Istituto Clinico Sant'Ambrogio, Via Luigi Giuseppe Faravelli, 16, 20149 Milan, Italy

[2] Department of Biomedical and Clinical Sciences, "Luigi Sacco" Hospital, University of Milan, Milan, Italy

BI and BII, and agree with Cai et al. [6], Ma et al. [8], and Xiong et al. [5] that reported a superiority of RY in terms of preventing bile reflux and remnant gastritis. Interestingly, no differences were found in terms of postoperative complications, time to resume oral intake, and risk of reflux esophagitis. [10–12] The results of such pairwise analyses were heterogeneous while a comprehensive analysis accounting for all types of surgical reconstruction after DG in the setting of randomized controlled trials (RCTs) is lacking.

This study aimed to perform a comprehensive and updated network meta-analysis comparing BI, BII, B-II Braun (BII Braun), RY, and Uncut Roux-en-Y (URY) after DG in the setting of RCT.

Materials and methods

A systematic review was performed according to the guidelines from the preferred reporting items for systematic reviews and network meta-analyses checklist (PRISMA-NMA) [13]. MEDLINE, Scopus, Web of Science, Cochrane Central Library, and ClinicalTrials.gov were used [14]. The last date of search was June 30th 2021. A combination of the following MeSH terms (Medical Subject Headings) were used ("distal gastrectomy" (tiab), OR "gastric reconstruction" (tiab)) AND ("Billroth I" (tiab), AND ("Billroth II" (tiab), OR "Billroth II-braun" (tiab)) AND ("Roux en Y" (tiab), OR "Uncut Roux en Y" (tiab)). All titles were evaluated and suitable abstracts extracted. The study protocol was registered at the PROSPERO (International prospective register of systematic reviews) (Registration Number: CRD42021283137).

Eligibility criteria

Inclusion criteria: (a) studies comparing surgical outcomes for Billroth I (BI), Billroth II (BII), Billroth II plus Braun (BII Braun), Roux-en-Y (RY), and uncut Roux-en-Y (URY) reconstruction after elective distal gastrectomy for cancer; (b) when two or more papers were published by the same institution, study group, or used the same dataset, articles with the longest follow-up or the largest sample size; (c) in case of duplicate studies with accumulating numbers of patients, only the most complete reports were included for quantitative analysis. Exclusion criteria: (a) they were not written in English; (b) the methodology or surgical technique was not clearly reported; (c) studies reporting mixed data including other surgical approaches (i.e., double tract reconstruction); (d) studies non-reporting any of the a priori defined primary outcomes; (e) studies published before 2000.

Data extraction

The following data were collected: author, year of publication, country, study design, number of patients, sex, age, body mass index (BMI), American Society of Anesthesiologists (ASA) score, comorbidities, surgical approach, postoperative surgical and oncologic outcomes. All data were computed independently by three investigators (AA, FL, AS) and compared at the end of the reviewing process. A fourth author (DB) reviewed the database and clarified discrepancies.

Definitions

Distal gastrectomy is defined as any method of anatomic surgical removal of distal stomach with associated lymphadenectomy. BI reconstruction is the formation of an end-to-end anastomosis between the proximal remnant stomach and duodenal stump. BII is an end-to-side anastomosis between the stomach and jejunum. BII Braun anastomosis is a side-to-side anastomosis between two segments of the jejunum performed about 25 cm distal to the gastrojejunostomy. It is designed to divert pancreatic juice and bile from the afferent limb, leading to decreased reflux into the stomach. RY was defined as gastrojejunostomy confectioned by side-to-end isoperistaltic anastomosis and the jejunal biliopancreatic limb was anastomosed end-to-side or side-to-side distal from the jejunal division as jejunojejunostomy. URY gastrojejunostomy is a modification of the Billroth II procedure with Braun anastomosis, in which a jejunal occlusion is fashioned.

Operative time: from first skin incision to complete skin closure (minutes); anastomotic leak: defined as clinical signs included peritonitis, fever, abdominal pain, pus discharge from the abdominal drain catheter, and/or contrast leakage from a viscus into a body cavity confirmed by a radiographic examination; delayed gastric emptying: (a) aspiration≥500ml/day from nasogastric tube left ≥ postoperative day 10, (b) reinsertion of nasogastric tube, (c) failure of unlimited oral intake by postoperative day 14; intraoperative blood loss: volume of blood loss during surgery (ml); postoperative mortality: defined as surgery-associated death within 30 days after operation; postoperative morbidity: defined as any complications occurring within 30 days after operation; reflux esophagitis: this was evaluated using the Los Angeles classification [15] and graded as grade 0 (absent) or 1 (present); remnant gastritis: evaluated on the basis of residue, gastritis, bile classification (RGB score [16]), normal mucosa (grade 0–grade 4; score≥grade 2 were positive findings) as postoperative

endoscopic findings 1 year after surgery. Outcomes were collected according to articles reporting.

Quality assessment

Three authors (AA, FL, AS) independently assessed the methodologic quality of the selected trials by using the Cochrane risk of bias tool [17]. This tool evaluates the following criteria: (1) method of randomization; (2) allocation concealment; (3) baseline comparability of study groups; and (4) blinding and completeness of follow-up. Trials were graded as having low (green circle), high (red circle), or unclear (yellow circle) risk of bias.

Outcomes of interest

Primary outcomes: anastomotic leak, anastomotic stricture, and overall complications (Clavien-Dindo >2). Secondary outcomes: postoperative bleeding requiring transfusion, surgical site infection (SSI), reoperation, intraoperative blood loss (ml), operative time (OT) (minutes), time to oral intake (days), hospital length of stay (HLOS) (days), 30-day mortality, and short-term functional finding (endoscopically proven esophagitis, bile reflux, and gastritis) at a minimum of 6 months after the index procedure. Postoperative complications were collected as articles reporting and according to the Clavien-Dindo classification. [18]

Statistical analysis

We performed a fully Bayesian network meta-analysis [19–21]. We used risk ratio (RR) as a pooled effect size measure for categorical outcomes and weighted mean difference (wmd) for continuous outcomes. Related to RR we adopted a "sceptical" prior distribution with mean and scale equal to 0 and 0.4, into an ordinary consistency binomial/log model. Assuming a common heterogeneity parameter across the treatment comparisons, we used an informative half-normal prior with zero mean and scale 0.5 or the between-study variability (τ) [18]. Sensitivity analysis regarding the choice of prior distribution for τ was considered [22]. Hazard ratio (HR) was calculated from the Kaplan-Meier data using a Cox proportional hazard model. Proportionality was tested with a Schoenfeld residual test and HR pooled according to Woods [23]. Statistical heterogeneity (I^2 index) was evaluated: value of 25% or smaller was defined as low heterogeneity, value between 50 and 75% as moderate heterogeneity, and 75% or larger as high heterogeneity [24]. The inference was performed using mean and relative 95% credible intervals (CrI), based on draws from marginal posterior distribution in Monte Carlo Markov chain (MCMC), simulating 300,000 iterations after a burn-in period of 30,000 iterations. We consider the estimated parameter statistical significant when its 95% CrI encompasses null-hypothesis value [25]. The plot of leverage values vs. the square root of the residual deviance was used to identify potential outlier [26]. The transitivity assumption was considered and descriptive statistics were generated to compare the distributions of baseline participant characteristics across studies and treatment comparisons. The confidence in estimates of the outcome was assessed using Confidence in Network Meta-Analysis (CINeMA) [27]. Statistical analyses were carried out using JAGS and R-Cran 3.4.3 (Distributed Statistical Computing; Vienna, Austria). [28, 29]

Results

Systematic review

The selection process flow chart is reported in Fig. 1. Initial search identified 295 publications. After removing duplicates, 25 titles and abstracts were reviewed. Further screening found 10 RCTs meeting the inclusion criteria. The included RCTs had issues regarding study design and blinding taking into consideration that the application of blinding into surgical RCTs is challenging. The method of randomization was described in all studies (i.e., computerized or sealed envelopes, etc.); the operating surgeon proficiency was reported in 5 RCTs while none was specified the power analysis (Supplementary Table 1).

Overall, 1456 patients were included in the analysis. Of these, 448 (33.7%) underwent BI, 220 (15.1%) BII, 114 BII Braun (7.8%), 533 (36.6%) RY, and 141 URY (9.6%) reconstruction (Table 1). The age of the patients ranged from 44 to 76 years old and the majority were males (65.6%). Patient BMI was reported in six studies and ranged from 20.1 to 25.9. Histology was reported in 898 patients; adenocarcinoma was diagnosed in 452 patients (50.3 %) while undifferentiated/diffused cancer was diagnosed in 393 patients (43.7%). Tumor size was reported in 4 studies and ranged from 1.3 to 7 cm. Pathologic tumor stage, according to 6th, 7th, and 8th edition of the American Joint Committee on Cancer and 14th Japanese Classifications of Gastric Carcinoma, was specified in 8 studies (1128 patients); Stage I: 52.3%, Stage II: 22.1%; Stage III: 22.7%, and Stage IV: 2.9%. There was no evidence of violation of the transitivity assumption, based on the observations that the common treatment (RY) was reasonably consistent across trials, effect modifiers were equally distributed across studies, and participants could in principle be randomized to any of the treatments being compared in the network. Finally, the design-by-treatment interaction model showed no evidence of statistically significant inconsistency (P=0.798). Descriptive statistics for all outcomes are reported in Table 2. The quality of included RCT is depicted in Supplementary Figure 1.

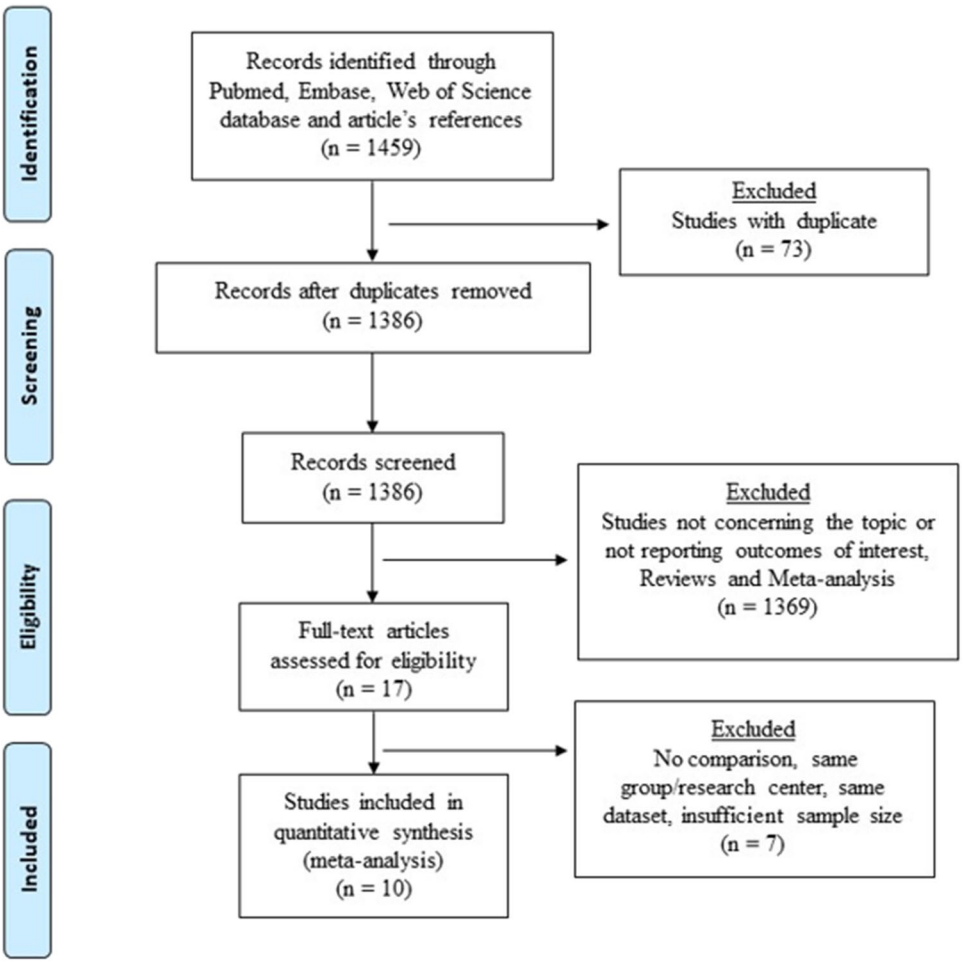

Fig. 1 The preferred reporting items for systematic reviews and network meta-analyses checklist (PRISMA-NMA) diagram

Network meta-analysis

Primary outcomes

Anastomotic leak was reported in 10 studies [30–39] (1456 patients) (Fig. 2A), with no significant differences when comparing RY vs. B-I (RR=0.52; 95% CrI 0.24–1.15), RY vs. B-II (RR=0.53; 95% CrI 0.19–1.56, RY vs. B-II Braun (RR=0.50; 95% CrI 0.17–1.5), and RY vs. URY (RR=0.65; 95% CrI 0.18–2.32). The related heterogeneity was 0.0 (0.0–24.6). Anastomotic stricture was reported in 8 studies [30–37] (1170 patients) (Fig. 2B), with no significant differences when comparing RY vs. B-I (RR=0.69; 95% CrI 0.3–1.48), RY vs. B-II (RR=0.83; 95% CrI 0.29–2.34), RY vs. B-II Braun (RR=0.7; 95% CrI 0.24–2.06), and RY vs. URY (RR=1.02; 95% CrI 0.28–3.68). The related heterogeneity was 0.0 (0.0–24.8). Ten studies [30–39] (1456 patients) reported overall morbidity (Fig. 2C) with no significant differences when comparing RY vs. B-I (RR=0.77; 95% CrI 0.53–1.15), Roux vs. B-II (RR=0.77; 95% CrI 0.45–1.37), RY vs. B-II Braun (RR=0.76; 95% CrI 0.38–1.51), and RY vs. URY (RR=1.18; 95% CrI 0.53–2.55). The treatment ranking evaluation graded RY as the surgical reconstruction technique with the lowest probability to be ranked as first treatment for anastomotic leak (13.5%), anastomotic stricture (32.8%), and overall complications (17.9%). The League table for primary outcomes with the related heterogeneity is depicted in Table 3.

Operative and perioperative outcomes

B-I was associated with a significantly shorter operative time (9 studies [30–33, 35–39]; 1416 patients) compared to RY (wmd= −24.3; 95% CrI −34.5; −14), B-II (wmd= −14.7; 95% CrI −28.5; −0.9), and B-II Braun (wmd= −27.4; 95% CrI −47.1; −7.9). No significant differences were found comparing RY vs. B-II (wmd= 9.6; 95% CrI −3.6; 22.9), RY vs. B-II Braun (wmd= −3.1; 95% CrI −23.7; 17.3), and RY vs. URY (wmd=8.5; 95% CrI −10.9; 28.0). Intraoperative blood loss (9 studies [30–37, 39]; 1294 patients) and time to oral intake (5 studies [30, 31, 33, 35, 38], 832 patients) were similar among different treatments. The risk of postoperative bleeding (7 studies [30–35, 37, 39], 990 patients) was significantly reduced in RY compared to B-I (RR=0.3; 95%

Table 1 Demographic and clinical characteristics of patients undergoing Billroth I (BI), Billroth II (BII), Billroth II Braun (BII Braun), Roux-en-Y (RY), and Uncut Roux-en-Y (URY). *yrs*, years; *BMI*, body mass index; *ADK*, adenocarcinoma; *UND*, undifferentiated; *nr*, not reported. Data are reported as numbers, mean ± standard deviation, median (range)

Author, year, country	Study design	Study period	Surgical techniques	No. patients	Mean age (yrs)	M/F	BMI (kg/m^2)	Stage I/II/III/IV	Histology ADK/ UND	Tumor size (cm)
Ishikawa et al., 2005, Japan [30]	RCT	2001–2004	BI	26	61±12.5	19/7	nr	13/12/1/0	nr	nr
			RY	24	64±9.25	17/7		10/6/7/1		
Lee et al., 2012, Korea [35]	RCT	2006–2007	BI	49	60±11.6	31/18	nr	nr	nr	nr
			BII Braun	52	59.7±10.9	49/13				
			RY	47	58.5±10.7	28/19				
Imamura et al., 2012, Japan [31]	RCT	2004–2009	BI	163	65±7.3	105/58	22.4±2.9	133/23/7/0	87/76	2.9±1.6
Hirao et al., 2013, Japan [40]			RY	169	65±8.6	115/54	22.5±2.8	130/24/10/5	90/79	3.0±1.6
Nakamura et al., 2016, Japan [32]	RCT	2009–2010	BI	60	66±10	40/20	nr	44/8/8/0	35/25	nr
			RY	62	67±9.25	45/17		45/8/9/0	38/24	
Kun Yang et al., 2017, China [33]	RCT	2011–2014	BI	70	56.3±10.7	40/30	22.4±3.1	30/14/23/3	13/57	3.6±1.9
			RY	70	54.9±11.5	47/23	22.7±3.5	21/17/25/4	10/60	4.4±2.6
Choi et al., 2017, Korea [34]	RCT	2011–2014	BI	20	62.4±8.9	16/4	24.7±3.6	17/2/1/0	nr	nr
			RY	20	62.8±9.3	10/10	26.6±4.3	19/1/0/0		
Dong Yang et al., 2017, China [37]	RCT	2015–2016	BII	79	61.8±11.4	54/25	nr	2/27/50/0	nr	nr
			URY	79	58.0±11.4	60/19		3/31/35/0		
Ren et al., 2019, China [36]	RCT	2016–2017	BI	60	47.14±1.33	32/28	23.1±1.2	nr	47/13	5.3±0.4
			BII	60	47.6±1.7	39/21	23.03±1.19		52/8	5.3±0.6
			RY	60	47.8±1.0	36/24	23.9±1.3		49/11	5.9±0.1
So et al., 2019, Singapore [38]	RCT	2008–2014	BII	81	62.0±10.9	46/35	23.3±4.1	29/22/26/4	nr	nr
			RY	81	64.5±10.9	45/36	24.3±4.2	25/27/26/3		
Wang et al., 2021, China [39]	RCT	2017–2018	BII Braun	62	54.69±10.1	44/18	22.4±3.1	0/37/25/0	15/23	3.3±1.1
			URY	62	54.84±8.31	44/18	22.4±3.1	0/36/26/0	16/17	3.4±1.2

Table 2 Descriptive statistics stratified according to different treatment. Billroth I (**B I**), Billroth II (**B II**), Billroth II Braun (**B II Braun**), Roux-en-Y (**RY**), Uncut Roux-en-Y (**URY**). *SSI*, surgical site infection; *DGE*, delayed gastric emptying; *HLOS*, hospital length of stay. Values are presented as percentages for categorical variables and as mean (range) for continuous variables

RY	BI I	BII	BII Braun	URY	
Categorical outcomes					
0.7 (0.0–2.4)	4.0 (0.0–21.6)	8.6 (1.2–25.0)	0.8 (0.0–1.9)	0.7 (0.0–1.2)	Anastomotic leak
0.5 (0.0–0.5)	0.5 (0.0–4.0)	2.5 (2.5–2.5)	1.7 (1.6–1.9)	0.2 (1.6–3.7)	Postoperative bleeding
0.2 (0.1–0.37)	0.1 (0.06–0.68)	0.3 (0.10–0.2)	0.08 (0.06–0.11)	0.06 (0.04–0.07)	Anastomotic stricture
1.4 (0.0–3.3)	3.9 (0.0–18.3)	10.0 (0.0–23.3)	1.7 (0.0–3.8)	0.7 (0.0–1.2)	SSI
1.5 (0.0–6.1)	0.0 (0.0.–0.0)	1.8 (0.0–3.7)	0.8 (0.0–1.6)	2.1 (1.2–3.2)	Reoperation
2.9 (0.0–5.7)	28.2 (12.8–55.1)	82.2 (82.2–82.2)	42.1 (14.5–75)	29.7 (0.0–53.1)	Bile reflux
9.2 (5.9–33.3)	16.4 (6.6–26.9)	-	19.2 (19.2–19.2)	-	Esophagitis
20.6 (0.0–35.4)	40.1 (11.6–63.3)	16.8 (13.5–21.5)	-	10.1 (10.1–10.1)	Remnant gastritis
20.0 (10.0–37.0)	17.8 (6.6–68.3)	37.2 (10.1–81.6)	8.7 (6.4–11.5)	6.3 (4.8–7.5)	Overall complications
0.2 (0.0–1.2)	0.0 (0.0–0.0)	1.2 (0.0–2.4)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	30-day mortality
0.12 (0.06–0.2)	0.05 (0.0–0–17)	0.43 (0.13–0.74)	-	0.84 (0.84–0.84)	Residual food
12.0 (6.4–20.8)	5.9 (0.0–17.1)	43.7 (13.5–74.6)	-	84.8 (84.8–84.8)	DGE
Continuous outcomes					
219.0 (67–432)	194.4 (84–374)	178.1 (74–315)	136.1 (83–198)	79.5 (74–86)	Intraoperative blood loss (ml)
237.4(211–271)	202 (163–250)	203.9 (155–247)	230.8 (211–247)	191.2 (145–249)	Operative time (minutes)
4.9 (3.8–11.5)	4.7 (4.1–6.5)	4.5 (3.9–5.0)	3.9 (3.9–3.9)	-	Time to oral intake (days)
12.0 (0.8–32)	10.8 (6.7–14)	10.1 (9.0–11.8)	7.3 (5.7–9.4)	5.6 (5.6–5.6)	HLOS (days)

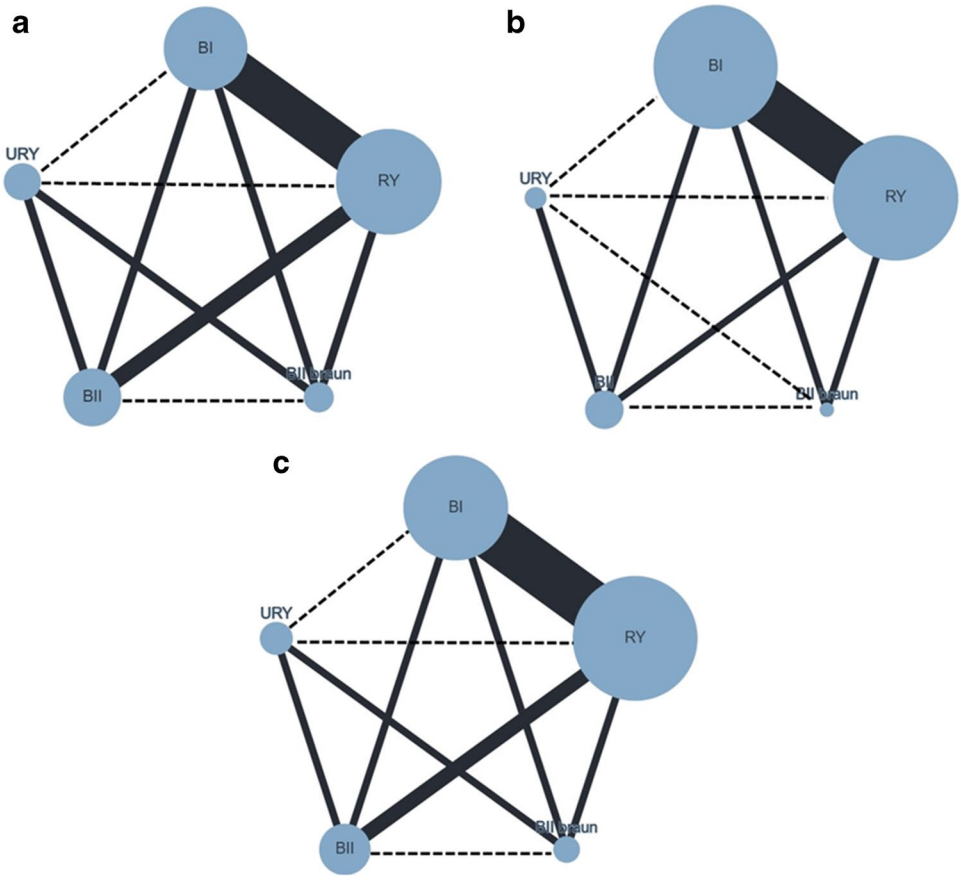

Fig. 2 Network geometry for primary outcomes: **A** anastomotic leak, **B** anastomotic stenosis, **C** overall complications. Nodes size reflects the sample size while edges width reflects the number of studies for a specific pairwise comparison. Billroth I (BI), Billroth II (BII), Billroth II Braun (BII Braun), Roux-en-Y (RY), and Uncut Roux-en-Y (URY)

Table 3 League table. Each row represents a specific outcome. Values in each column represent the relative effect of the referral treatment (bold) with the comparator. Values are expressed as risk ratio (RR) and 95% credible intervals (95%CrI). I^2: heterogeneity. Table Legend: BI: Billroth I, BII: Billroth II, BII Braun: Billroth II Braun, RY: Roux-en-Y, and URY: Uncut Roux-en-Y. *SSI*, surgical site infection; *DGE*, delayed gastric emptying; *HLOS*, hospital length of stay

Categorical variables					I^2 (95%CrI)	**Outcomes**
BI	0.97 (0.46-2.05)	1.04 (0.48-2.22)	0.52 (0.24-1.15)	0.80 (0.28-2.34)	0.0 (0.0–24.6)	**Anastomotic leak**
1.02 (0.48–2.15)	**BII**	1.06 (0.37–3.03)	0.53 (0.19–1.56)	0.82 (0.38–1.78)		
0.96 (0.44–2.04)	0.93 (0.32–2.67)	**BII Braun**	0.50 (0.17–1.50)	0.77 (0.21–2.80)		
1.90 (0.86–4.15)	1.86 (0.64–5.24)	1.98 (0.66–5.83)	**RY**	1.53 (0.42–5.34)		
1.25 (0.42–3.56)	1.21 (0.55–2.62)	1.29 (0.35–4.65)	0.65 (0.18–2.32)	**URY**		
BI	0.51 (0.13–1.96)	0.53 (0.25–1.17)	0.30 (0.11–0.93)	0.46 (0.14–1.46)	78.3 (65.4–81.2)	**Postoperative bleeding**
1.96 (0.50–7.22)	**BII**	1.04 (0.35–3.03)	0.60 (0.16–2.22)	0.90 (0.42–1.94)		
1.87 (0.84–3.97)	0.95 (0.32–2.78)	**BII Braun**	0.57 (0.27–1.23)	0.86 (0.39–1.88)		
3.29 (1.07–8.72)	1.66 (0.44–5.97)	1.74 (0.80–3.61)	**RY**	1.49 (0.52–4.22)		
2.16 (0.68–6.78)	1.11 (0.51–2.38)	1.16 (0.53–2.51)	0.66 (0.23–1.89)	**URY**		
BI	0.83 (0.38–1.82)	0.98 (0.45–2.11)	0.69 (0.3–1.48)	0.68 (0.22–2.05)	0.0 (0.0–24.8)	**Anastomotic stricture**
1.19 (0.54–2.58)	**BII**	1.17 (0.40–3.44)	0.83 (0.29–2.39)	0.81 (0.37–1.77)		
1.01 (0.47–2.17)	0.84 (0.29–2.48)	**BII Braun**	0.70 (0.24–2.06)	0.69 (0.18–2.59)		
1.43 (0.67–2.99)	1.19 (0.41–3.40)	1.41 (0.48–4.03)	**RY**	0.97 (0.27–3.54)		
1.46 (0.48–4.37)	1.22 (0.56–2.65)	1.44 (0.38–5.34)	1.02 (0.28–3.68)	**URY**		
BI	0.91 (0.44–1.92)	1.09 (0.52–2.31)	0.58 (0.27–1.28)	0.70 (0.24–2.06)	0.0 (0.0–32.1)	**SSI**
1.08 (0.52–2.26)	**BII**	1.19 (0.42–3.33)	0.63 (0.22–1.83)	0.77 (0.35–1.68)		
0.91 (0.43–1.91)	0.83 (0.3–2.34)	**BII Braun**	0.53 (0.18–1.57)	0.64 (0.18–2.31)		
1.70 (0.77–3.66)	1.58 (0.54–4.35)	1.88 (0.63–5.37)	**RY**	1.21 (0.35–4.11)		
1.41 (0.48–4.01)	1.29 ()0.59–2.81)	1.55 (0.43–5.39)	0.82 (0.24–2.85)	**URY**		
BI	0.88 (0.41–1.88)	0.94 (0.44–2.01)	0.66 (0.31–1.43)	0.76 (0.26–2.24)	0.0 (0.0–28.7)	**Reoperation**
1.13 (0.53–2.39)	**BII**	1.06 (0.37–3.01)	0.75 (0.27–2.12)	0.86 (0.40–1.87)		
1.06 (0.49–2.26)	0.93 (0.32–2.67)	**BII Braun**	0.70 (0.24–2.05)	0.81 (0.22–2.92)		
1.49 (0.69–3.16)	1.32 (0.47–3.65)	1.41 (0.48–4.02)	**RY**	1.15 (0.32–4.01)		
1.3 (0.44–3.74)	1.15 (0.53–2.46)	1.22 (0.34–4.35)	0.86 (2.24–3.04)	**URY**		
BI	0.64 (0.17–2.44)	0.73 (0.35–1.55)	0.48 (0.17–1.41)	0.62 (0.21–1.88)	91.3 (80.1–100)	**Bile reflux**
1.55 (0.40–5.77)	**BII**	1.14 (0.38–3.36)	0.74 (0.20–2.81)	0.97 (0.45–2.10)		
1.36 (0.64–2.83)	0.87 (0.29–2.60)	**BII Braun**	0.65 (0.30–1.43)	0.85 (0.39–1.87)		
2.08 (0.70–5.75)	1.33 (0.35–4.93)	1.51 (0.69–3.28)	**RY**	1.30 (0.44–3.76)		
1.59 (0.53–4.67)	1.02 (0.47–2.20)	1.16 (0.53–2.53)	0.76 (0.26–2.2)	**URY**		
BI	-	0.91 (0.19–4.90)	0.58 (0.24–1.51)	-	43.3 (31.2–56.5)	**Esophagitis**
-	**BII**	-	-	-		
1.09 (0.20–5.15)	-	**BII Braun**	0.63 (0.11–3.23)	-		
1.70 (0.66–4.11)	-	1.56 (0.30–8.38)	**RY**	-		
-	-	-	-	**URY**		
BI	1.18 (0.53–2.48)	-	0.56 (0.35–0.76)	0.51 (0.14–1.71)	0.3 (0.0–21.9)	**Remnant gastritis**
0.84 (0.40–1.85)	**BII**	-	0.47 (0.22–0.97)	0.43 (0.15–1.13)		
-	-	**BII Braun**	-	-		
1.77 (1.30–2.78)	2.10 (1.02–4.51)	-	**RY**	0.91 (0.26–3.11)		
1.94 (0.58–7.12)	2.28 (0.88–6.44)	-	1.08 (0.32–3.77)	**URY**		
BI	1.01 (0.59–1.64)	1.02 (0.56–1.87)	0.77 (0.53–1.15)	0.65 (0.31–1.42)	59.2 (45.6–73.4)	**Overall complications**
0.99 (0.60–1.66)	**BII**	1.17 (0.40–3.44)	0.77 (0.45–1.37)	0.65 (0.35–1.25)		
0.97 (0.53–1.78)	0.98 (0.46–2.01)	**BII Braun**	0.76 (0.38–1.51)	0.64 (0.27–1.52)		
1.28 (0.86–1.86)	1.29 (0.72–2.18)	1.31 (0.66–2.59)	**RY**	0.84 (0.39–1.87)		
1.52 (0.70–3.17)	1.52 (0.79–2.83)	1.55 (0.65–3.61)	1.18 (0.53–2.55)	**URY**		

Table 3 (continued)

Categorical variables					I^2 (95%CrI)	**Outcomes**
BI	2.02 (0.32–19.32)	-	1.84 (0.82–6.38)	2.26 (0.21–39.05)	42.1 (35.6–52.1)	**DGE**
0.49 (0.05–3.06)	**BII**	-	0.92 (0.15–5.44)	1.13 (0.22–5.83)		
-	-	**BII Braun**	-	-		
0.53 (0.15–1.21)	1.08 (0.18–6.32)	-	**RY**	1.22 (0.11–13.55)		
0.44 (0.02–4.73)	0.88 (0.17–4.54)	-	0.81 (0.07–9.03)	**URY**		
BI	0.72 (0.24–2.16)	0.75 (0.25–2.25)	0.73 (0.33–1.61)	0.60 (0.15–2.33)	61.6 (48.2–75.9)	**30-day mortality**
1.38 (0.46–4.11)	**BII**	1.04 (0.35–3.08)	1.02 (0.47–2.20)	0.84 (0.38–1.82)		
1.32 (0.44–3.19)	0.95 (0.32–2.81)	**BII Braun**	0.97 (0.45–2.11)	0.80 (0.21–2.98)		
1.35 (0.61–2.94)	0.97 (0.45–2.11)	1.02 (0.47–2.21)	**RY**	0.82 (0.27–2.42)		
1.64 (0.42–6.32)	1.19 (0.54–2.58)	1.24 (0.33–4.64)	1.21 (0.41–3.60)	**URY**		
Continuous variables	**I2 (95%CrI)**	**Outcomes**				
BI	3.7 (−11.2; 19.7)	5.7 (−23.6; 36.3)	8.0 (−2.7;19.6)	5.4 (−16.5;28.9)	54.1 (41.3–69.7)	**Intraoperative blood loss (ml)**
−3.7 (−19.7; 11.2)	**BII**	1.9 (−25.1; 29.5)	4.2 (−11.2;19.7)	1.6 (15.4;19.4)		
−5.7 (−36.3; 23.6)	−1.9 (−29.5; 25.1)	**BII Braun**	2.3 (−27.9;31.8)	−0.2 (−23.0; 22.3)		
−8.0 (−19.6; 2.7)	−4.2 (−19.7; 11.2)	−2.3 (−31.8; 27.9)	**RY**	−2.6 (−24.9; 20.4)		
−5.4 (−28.9; 16.5)	−1.6 (−19.4; 15.4)	0.2 (−22.3; 23.1)	2.6 (−20.4; 24.9)	**URY**		
BI	14.7 (0.9; 28.5)	27.4 (7.9; 47.1)	24.3 (14.2; 34.5)	15.7 (−3.4; 35.2)	95.6 (81.2–100.0)	**Operative time (minutes)**
−14.7 (−28.5;−0.9)	**BII**	12.7 (−7.3; 33.0)	9.6 (−3.6; 22.9)	1.0 (−15.4;17.6)		
−27.4 (−47.1;−7.9)	−12.7 (−33.0; 7.3)	**BII Braun**	−3.1 (−23.7; 17.3)	−11.7 (−30.0; 6.6)		
−24.3 (−34.5;−14)	−9.6 (−22.9; 3.6)	3.1 (−17.3; 23.7)	**RY**	−8.5 (−28.0; 10.9)		
−15.7 (−35.2; 3.4)	−1.0 (−17.6; 15.4)	11.7 (−6.6; 30.0)	8.5 (−10.9; 28.0)	**URY**		
BI	1.1 (−9.3;11.5)	0.3 (−8.1; 8.7)	1.1 (−3.5; 5.8)	-	95.0 (84.3–100.0)	**Time to oral intake (days)**
−1. (−11.5; 9.3)	**BII**	−0.7 (−13.3; 11.7)	0.0 (−9.2; 9.3)	-		
−0.3 (−8.7; 8.1)	0.7 (−11.7; 13.3)	**BII Braun**	0.7 (−7.6; 9.2)	-		
−1.1 (−5.8; 3.5)	−0.0 (−9.3; 9.2)	−0.7 (−9.2; 7.6)	**RY**	-		
-	-	**-**	-	**URY**		
BI	3.5 (−6.7; 14.1)	5.3 (−7.5; 18.6)	2.2 (−3.1; 8.1)	5.2 (−14.3; 25.0)	89.5 (76.5–100.0)	**HLOS (days)**
−3.5 (−14.1; 6.7)	**BII**	1.8 (−14.2; 17.8)	−1.2 (−10.9; 8.5)	1.7 (−20.0; 23.4)		
−5.3 (−18.6; 7.5)	−1.8 (−17.8; 14.2)	**BII Braun**	−3.1 (−16.1; 10.0)	−0.1 (−14.8; 14.5)		
−2.2 (−8.1; 3.1)	1.2 (−8.5; 10.9)	3.1 (−10.1; 16.1)	**RY**	3.0 (−16.8; 22.6)		
−5.2 (−25.0; 14.3)	−1.7 (−23.4; 20.0)	0.1 (−14.5; 14.8)	−3.0 (−22.6; 16.8)	**URY**		

Crl 0.11;0.93). No significant differences were found in term of HLOS (9 studies [30–36, 38, 39] 1298 patients), SSI (7 studies [31–33, 35–37, 39], 1204 patients) reoperation (8 studies [31, 33–39], 1284 patients), and 30-day mortality (6 studies [31, 33, 35, 35, 37, 37–39], 1064 patients).

Short-term functional outcomes

At a short-term follow-up (12 months), RY reconstruction was associated with a significantly reduced risk of remnant gastritis (6 studies [30, 32, 33, 36–38, 40]; 964 patients) compared to BI (RR=0.56; 95% Crl 0.35–0.76) and BII reconstruction (RR=0.47; 95% Crl 0.22–0.97) but equivalent risk compared to URY (RR=1.08; 95% Crl 0.32–3.77). Despite the lack of statistically significant differences, there was a trend toward reduced risk of bile reflux (6 studies [30, 32, 33, 35, 37, 39]; 742 patients) for RY compared to BI (RR=0.48; 95% Crl 0.17–1.41), BII (RR=0.74; 95% Crl 0.20–2.81), BII Braun (RR=0.65; 95% Crl 0.30–1.43), and URY (RR=0.76; 95% Crl 0.26–2.21). Similarly, there was a trend toward reduced risk of endoscopically confirmed esophagitis (3 studies [31, 32, 35]; 602 patients) for RY compared to BI (RR=0.58; 95% Crl 0.24–1.51) and BII Braun (RR=0.63; 95% Crl 0.11–3.23). No significant differences were observed among treatments in the setting of delayed gastric emptying (6 studies [30–34, 38]; 964 patients). The treatment ranking evaluation ranked RY as the treatment with the lowest probability to be ranked as the treatment

with the higher probability for remnant gastritis (11%), bile reflux (22%), and esophagitis (12%). The League table for secondary outcomes with related between study heterogeneity is reported in Table 3.

Discussion

This network meta-analysis shows that there are five principal options for reconstruction and intestinal anastomosis after distal gastrectomy. All the techniques seem equivalent in terms of anastomotic leak, anastomotic stricture, and overall morbidity. No significant differences were found in terms of short-term surgical outcomes except a significantly shorter operative time for BI reconstruction. At short-term follow-up (12-month), RY seems associated with a significantly reduced risk of remnant gastritis with a trend toward reduced risk of esophagitis and bile reflux compared to BI and BII while no differences were found in terms of delayed gastric emptying.

In Eastern countries, BI gastroduodenostomy, when technically feasible, is usually performed after distal gastric resection because of its simplicity and as it maintains the physiological passage of food into the duodenum [41]. Similarly, BII reconstruction is often used when BI is technically unfeasible because of anastomotic tension. Principal drawback of BI and BII anastomoses is the chronic bile reflux into the remnant with consequent alteration of the physiologic gastric acid environment [42]. This may cause esophagitis, Barrett's esophagus, and remnant gastritis [43]. B-II Braun anastomosis has been described in attempt to theoretically reduce the incidence of bile reflux into the remnant. Similarly, the RY and URY techniques mainly performed in Western countries have been introduced with the purpose to reduce the risk of bile reflux. However, they are more complicated to perform and the access to the Vater's papilla during endoscopic retrograde cholangiopancreatography (ERCP) is challenging. Furthermore, some patients may develop functional Roux limb obstruction (Roux stasis syndrome) [44] with a potential risk for internal hernia (Petersen's hernia) [44]. Controversy still exists regarding which is the best method for reconstruction after distal gastrectomy while a definitive indication is lacking. Previous studies and pairwise analyses have been published; however, a comprehensive description of the best evidence including direct and indirect comparison is lacking.

The incidence of anastomotic leak after distal gastrectomy has been reported up to 2.7% [45]. In the present systematic review, BI, BII, BII Braun, RY, and URY anastomoses were associated with 4.0%, 8.6%, 0.8%, 0.7%, and 0.7% leak rate, respectively. No statistically significant differences were observed among the different treatments with a 0.0% related heterogeneity. This is similar to He et al. that reported a comparable leak risk comparing RY and BI [11]. Despite the lack of significance, the point estimation of RY was below 1.00 thus reflecting a trend toward reduced postoperative leak risk. This is further corroborated by the treatment ranking evaluation that graded RY as the reconstruction technique with the lowest probability to be ranked as first treatment for anastomotic leak (13.5%). No significant differences were found in terms of anastomotic stricture, overall complication, and 30-day mortality among the considered treatments. This is in line with previous studies thus reflecting the comparable safety profile of all these surgical approaches. Again, despite the lack of statistical significance, the treatment ranking evaluation graded RY as the reconstruction technique with the lowest probability to be ranked as first treatment for anastomotic stricture (32.8%), overall complications (17.9%), and 30-day mortality (31.4%). The heterogeneity was 0.0% for anastomotic leak, structure, and 30-day mortality thus adding robustness to the results. Despite the low heterogeneity, patient selection bias, preoperative comorbidities, institutional operative volume, surgeon experience, and learning curve should be considered and may constitute a source of confounding.

Operative time was significantly reduced for BI anastomosis. This is explained by the additional time used to perform other anastomoses in BII, BII Braun, RY, and URY reconstruction. Different from previously published studies that reported reduced intraoperative bleeding for BI and BII [46], intraoperative bleeding was similar among treatments. This may be explained by the increasing use of energy devices during mesentery separation and vessels cauterization. The related heterogeneity was moderate (54%). and therefore may be influenced by overtime refinement of technique, different surgical approach (open vs. minimally invasive), increased use of stapling and energy devices, operating surgeon experience, and hospital volume.

This meta-analysis showed that RY anastomosis seems superior to BI, BII, and BII Braun in reducing the risk of remnant gastritis. Despite the lack of statistical significance, RY anastomosis was also associated with a trend toward reduced bile reflux and endoscopically diagnosed esophagitis as the point estimation of both outcomes was below 1.00. This is attributable to the "Y" limb configuration that, when adequately fashioned, may prevent the alkaline bile reflux into the remnant. This is in accordance with Prassana et al. [47] that found a significantly reduced risk of duodenal reflux after RY. Interestingly and in accordance with Chan et al., BII Braun was not associated with a reduced risk of remnant gastritis and bile reflux [48]. The chronic duodenal reflux has been reported to be associated with significant histologic mucosal changes (intestinal metaplasia), genomic alterations (increased expression of a mutant form of protein p53), and consequent increased risk of remnant adenocarcinoma (OR=1.48) [49]. Notably, all the included

RCTs reported functional data up to 12-month follow-up; therefore, all are limited by short-term evaluation. Further analyses are therefore mandatory to deepen this trend in the long term. The global heterogeneity for such functional outcomes was moderate-high mainly because of the preoperative patient's characteristics, treatment methods, postoperative monitoring, and different operating surgeon experience and distance from gastrojejunostomy and jejunojejunostomy (<30 cm or >30cm) [35]. Although we try to control for some potential covariates, we cannot adjust our analysis of all of these confounders. It should be finally noted that all these functional outcomes were endoscopically assessed therefore further functional studies (i.e., 24-h pH-impedance study) may be useful to deepen the clinical relevance of this finding. Therefore, this meta-analysis also intends to plea for further qualitative and standardized studies to objectively address this issue and further appraise medium- and long-term outcomes.

No significant differences were found in terms of delayed gastric emptying among treatments. This is in accordance with He et al. [11] but is different from previously published analyses that reported a higher incidence of delayed gastric emptying after RY reconstruction (Roux stasis syndrome) [8]. This syndrome is characterized by abdominal pain, vomiting, and nausea after oral intake of food. Rather than a mechanical obstruction, this syndrome seems likely to be associated with a functional obstruction of the "Y" limb possibly increased by a >40 cm limb length. Furthermore, it is possible that the altered intestinal continuity and intestinal innervation may cause an altered electrical stimulation with a retrograde peristalsis in the efferent "Y" limb responsible for the functional obstruction. Although these factors result in delayed gastric emptying, the exact incidence and reason of Roux stasis syndrome are also debatable.

To our knowledge, this is the first systematic review and network analysis that includes all RCTs of this topic that have been published up to date. Using network meta-analytical techniques, we were able to globally synthesize data from numerous studies and therefore rank the treatments. The study was planned in agreement with PRISMA guidelines, and it followed a rigorous methodology that was a priori stated in the PROSPERO protocol. This included comprehensive outcome measures and the evaluation of quality at study level (risk of bias) and confidence in results at outcome level (CINeMA). The selection criteria led to a homogenous population for some of the primary outcomes, as confirmed by low heterogeneity. This study had several limitations. First, although transitivity assumption was met with no evidence of statistically significant inconsistency in the network analysis, the accuracy of our results can be tempered by differences in surgical approach (open vs. minimally invasive) with a potential effect on postoperative outcomes (postoperative pain, HLOS, time to oral intake) and complications. Therefore, further evaluations are necessary to deeply assess outcomes after sub analysis according to the different surgical approach (open vs. minimally invasive) and anastomotic technique (i.e., linear stapler, circular stapler, or hand-sewn). Second, even only RCTs were included in this review, the quality of evidence remained moderate, in part, due to the lack of patient and surgeon blinding, the limited power of some trials, different method for randomization, and quality control. Third, because included RCT were performed by expert surgeons in high-volume referral centers, results may not be generalizable to small community hospitals. Fourth, all included studies were performed in Eastern countries and may be less pertinent to Wester settings. Fifth, use of analgesics, residual ingested food, postoperative nutritional status, patients' satisfaction, quality of life, and return to normal/daily activities were heterogeneously or marginally evaluated in the included studies; therefore, a robust quantitative analysis was unfeasible. Lastly, the short-term analysis evidence mandates future investigational trials with a medium- and long-term outcome assessment.

Conclusions

This network meta-analysis, comparing five different options for reconstruction and intestinal anastomosis after distal gastrectomy, showed that all techniques seem equally safe with comparable anastomotic leak, anastomotic stricture, overall morbidity and mortality. In the short-term follow-up, RY seems associated with a reduced risk of remnant gastritis and a trend toward a reduced risk of bile reflux and endoscopically proven esophagitis. Since the related heterogeneity of these functional outcomes is moderate-high, further studies are warranted to clinically and objectively assess these results in the medium and long run.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00423-021-02411-6.

Declarations

Conflict of Interest The authors declare no competing interests.

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