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REVIEW ARTICLE

Effect of gastric ischemic conditioning prior to esophagectomy: systematic review and meta-analysis

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Abstract

Ischemia at the anastomotic site is thought to be a protagonist in the development of anastomosis-related complications while different strategies to overcome this problem have been reported. Gastric ischemic conditioning (GIC) prior to esophagectomy has been described with this intent. Evaluate the effect of GIC on anastomotic complications after esophagectomy. Scopus, Web of Science, MEDLINE, and PubMed were investigated up to March 31st, 2023. We considered articles that appraised short-term outcomes after GIC vs. no GIC in patients undergoing esophagectomy. Anastomotic leak (AL), anastomotic stricture (AS), and gastric conduit necrosis (GCN) were primary outcomes. Risk ratio (RR) and standardized mean difference (SMD) were used as pooled effect size measures, whereas 95% confidence intervals (95% CIs) were used to calculate related inference. Fourteen studies (1760 patients) were included. Of those, 732 (41.6%) underwent GIC, while 1028 (58.4%) underwent one-step esophagectomy. Compared with no GIC, GIC was related to a reduced RR for AL (R RR = 0.63; 95% CI 0.47–0.86; $p < 0.01$) and AS (RR = 0.51; 95% CI 0.29–0.91; $p = 0.02$), whereas no differences were found for GCN (RR = 0.56; 95% CI 0.19–1.61; $p = 0.28$). Postoperative pneumonia (RR = 1.09; $p = 0.99$), overall complications (RR = 0.87; $p = 0.19$), operative time (SMD −0.58; $p = 0.07$), hospital stay (SMD 0.66; $p = 0.09$), and 30-day mortality (RR = 0.69; $p = 0.22$) were comparable. GIC prior to esophagectomy seems associated with a reduced risk for AL and AS. Further studies are necessary to identify the subset of patients who can benefit from this procedure, the optimal technique, and the timing of GIC prior to esophagectomy.

Keywords Esophagectomy · Ischemic conditioning · Laparoscopy · Embolization · Outcomes

Introduction

Esophagectomy, lymphadenectomy and restoration of the gastrointestinal continuity via gastric conduit reconstruction represent the gold standard treatment for esophageal malignancies [1]. Anastomotic leak (AL) remains the most feared complication, potentially occurring in up to 40% of patients [2, 3]. Increase in mortality, prolonged hospital stay, delayed oral feeding, risk of reintervention, increased risk of recurrence, and decrease of overall/disease-free survival have been reported to be associated with AL [4, 5]. Anastomotic stricture (AS) may occur in up to 30% of patients and may require endoscopic dilation with a negative effect of postoperative recovery, nutritional status, and quality of life [6].

Gastric ischemic conditioning (GIC) prior to esophagectomy may be an option to improve blood flow in the tubulized stomach and thus decrease the risk of ischemia and subsequent development of AL and AS [7, 8]. Technically, the partial devascularization of the stomach may determine a progressive vascular adaptation with improvement of the submucosal vascular network at the anastomotic site [9, 10]. Previous animal studies described improvement of fundic perfusion, while studies on human suggested a conceivable

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encouraging effect of preoperative GIC with reduced risk of AL and AS [11–16]. Previous meta-analyses have been published with conflicting results, because methodological flaws due to inclusion of single arm studies, search strategies incongruities, inclusion of duplicates with patient overlap, and substantial between-study heterogeneity [17–20]. Further, there is no consensus on the optimal technique and timing from GIC to esophagectomy.

The aim of our present work was to conduct an updated systematic review to evaluate the effect of GIC on anastomotic complications after esophagectomy.

Materials and methods

We conducted this study according to the Preferred Reporting Items For Systematic Reviews and Meta-Analyses (PRISMA) statement and MOOSE guidelines [21, 22]. All authors of GIC International Collaborative Group agreed on the study protocol.

Institutional review board approval was not required. PubMed, MEDLINE, Scopus, Web of Science, Cochrane Central Library, and ClinicalTrials.gov were used [23]. The last date of search was the March 31st, 2023. A combination of the following MeSH terms (Medical Subject Headings) was used ("esophagectomy" (tiab), OR "esophagectomies" (tiab), OR, "esophagogastric" (tiab), OR "esoph*"(tiab)) AND ("anastomosis" (tiab), OR "suture" (tiab)) AND ("ischemic conditioning" (tiab), OR "ischemic preconditioning" (tiab)) AND ("outcomes" (tiab), OR "complication" (tiab)) AND ("leak" (tiab), OR "leakage" (tiab)) AND ("stricture" (tiab), OR "stenosis" (tiab)). All titles were evaluated and suitable abstracts extracted. The search was completed by consulting the references of each article. The study protocol was registered at the PROSPERO (International prospective register of systematic reviews) (Registration Number: CRD42023423153).

Eligibility criteria

Inclusion criteria: (a) cohort studies and randomized controlled trials (RCTs) comparing outcomes for GIC vs. no GIC among adult patients (> 18 year old) undergoing elective esophagectomy; (b) English written; (c) when two or more papers were published by the same institution, study group, or used the same data-set, articles with the longest follow-up or the largest sample size; (d) in case of duplicate studies with accumulating numbers of patients only the most complete reports were included for quantitative analysis. Exclusion criteria: (a) not English-written; (b) no clear outcome distinction between GIC vs. no GIC; (d) articles with less than five patients per study arm.

Data extraction

The following data were collected: authors, year of publication, country, study design, number of patients, sex, age, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status, comorbidities, surgical indication, tumor characteristics, histological type, tumor location, cancer stage, neoadjuvant chemoradiotherapy, type of GIC (angioembolization vs. surgery), target vessels, timing from GIC to esophagectomy and postoperative outcomes. All data were computed independently by four investigators (AA, DB, GB, LB) and compared at the end of the reviewing process to determined discrepancies.

Outcomes

Primary outcomes were postoperative AL, AS, and gastric conduit necrosis (GCN). Secondary outcomes were pulmonary complications, overall complications, operative time (OT) (minutes), intensive care unit (ICU) length of stay, hospital length of stay (HLOS) (days) and 30-day mortality. AL was defined as evidence of contrast extravasation at postoperative swallow study and/or CT-scan, or endoscopic visualization of anastomotic dehiscence/fistula, or visible loss of digestive secretions through surgical drains combined with clinical signs. AS was defined based on the need for endoscopic dilatation up to 6 months after the operation. GCN was defined as severe ischemia of the upper gastric conduit necessitating resection and diversion or refashioning of the anastomosis.

Quality assessment

Three authors (AA, AS, LC) independently assessed the methodological quality of included studies. The ROBINS-I tool was used for observational studies [24]. The following domains were considered: confounding bias, selection bias, classification bias, intervention bias, missing data bias, outcomes measurement bias, and reporting bias. Each domain is evaluated with one of the following: "yes", "probably yes", "probably no", or "no". The categories of judgement for each study are low, moderate, serious, and critical risk of bias. The methodological quality of Randomized Controlled Trials (RCTs) was appraised with the Cochrane risk of bias tool [25]. 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 follows: A = adequate, B = unclear, and C = inadequate on each criterion. Thus, each RCT was graded as having low, moderate, or high risk of bias. Disagreements were solved by discussion. We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool to assess the quality of the body of evidence across studies [26].

Statistical analysis

The results of the systematic review were summarized quantitatively into frequentist random effect meta-analysis of pooled Risk Ratio (RR) and standardized mean difference (SMD). An inverse-variance method and DerSimonian–Laird estimator for the variance of the true effect size (τ^2) were performed [27]. Heterogeneity among studies was evaluated by the I^2 index and Cochran's Q test [28]. Statistical heterogeneity was considered low, moderate, and high for I^2 values of 25, 50, and 75%, respectively, and significant when $p < 0.10$ [29, 30]. The Wald-type 95% confidence interval (CI) was computed for pooled measurements; otherwise, the 95% CI for the I^2 index was calculated according to Higgins and Thompson [31, 32]. The prediction interval for the treatment effect of a new study was calculated according to Borestein [28]. As the sample size was not the same in all studies, we performed a sensitivity analysis by excluding one study each time and rerunning the analysis to verify the robustness of the overall results. The publication bias was also investigated with the Trim and Fill funnel plot and Egger test. A two-sided p value was considered statistically significant when $p < 0.05$. All analyses and figures were carried out using the R software program, version 3.2.2 [33].

Results

Systematic review

The PRISMA flowchart is reported in Fig. 1. Overall, 1807 publications were identified. After duplicates removal, 1106 titles were screened. Overall, 291 abstracts were reviewed, while 58 articles were found possibly relevant for full-text assessment. After full-text evaluation, 14 studies meet the inclusion/exclusion criteria and were included in the quantitative synthesis. Thirteen studies were retrospective in design, and one study was a RCT. The quality of observational studies and RCTs is reported in Supplementary Table 1 and Supplementary Fig. 1.

Overall, 1760 patients were included (Table 1). Of those, 732 (41.6%) underwent GIC, while 1028 (58.4%) underwent one-step esophagectomy. The age of the patient population ranged from 24 to 84 years, the BMI ranged from 15.6 to 46 kg/m^2 and the majority (82.1%) were males. Tumor location was reported in three studies. Tumor histology was specified in 8 studies; adenocarcinoma and squamous cell carcinoma were diagnosed in 75% and 25% of patients, respectively. Pathological tumor staging according to the 7th and 8th edition of the American Joint Committee on Cancer (AJCC) and Japanese gastric cancer classification (JGCC) was detailed in 5 studies (Stage 0–I: 21.1%, Stage II: 29.7%; Stage III: 49%, and Stage IV: 0.2%). Open, hybrid or totally minimally invasive esophagectomy were performed depending on operating surgeon preference and expertise. A cervical or intrathoracic anastomosis was performed according to tumor location, operating surgeon preferences, and oncological principles. The use of neoadjuvant chemoradiation therapy was heterogeneously reported in 11 studies (i.e. protocols, regimens, etc.). The extent of lymphadenectomy (2-filed and 3-field) was specified in 5 studies and varied depending on surgeon expertise and tumor clinical stage/location.

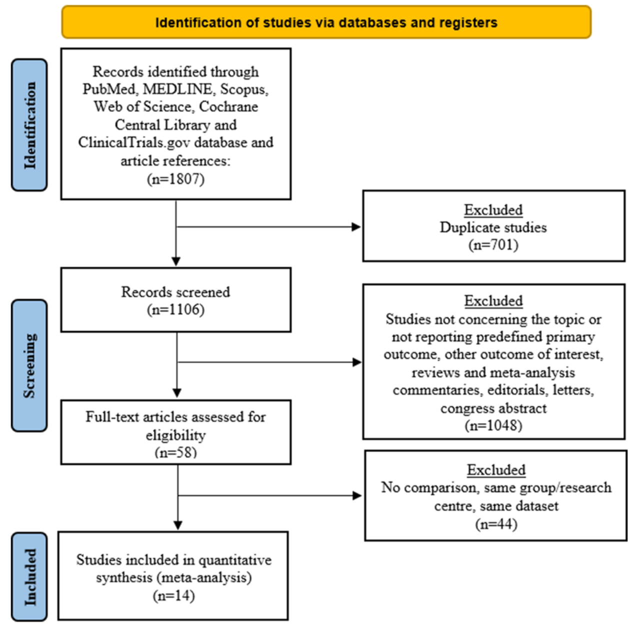

Fig. 1 The preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram

Laparoscopic GIC was performed in 593 (81%) and angioembolization in 139 (19%) patients. Multi-vessel GIC with ligation of the left gastric artery, short gastric vessels, and right gastric artery or single vessel GIC with selective ligation of the left gastric artery were performed in 442 (60.3%) and 290 (39.7%) patients, respectively. The time from GIC to esophagectomy varied from 3 to 196 days.

Meta-analysis—primary outcomes

AL was reported in 14 studies (1760 patients). The cumulative incidence of AL was reduced for GIC vs. no GIC (8.8% vs. 14.4%). Compared to no GIC, GIC was associated with a significantly reduced AL risk (RR = 0.63; 95% CI 0.47–0.86; $p < 0.01$) (Fig. 2A). The prediction lower and upper limits

Table 1 Demographic, clinical, and operative data for patients undergoing gastric ischemic conditioning (GIC) before esophagectomy and one stage esophagectomy (C, control)

Author, year, country	Study design	Group	Size, *n*	Age (years)	Male	BMI kg/m^2	Neoadjuvant treatment	GIC method	Vessels	GIC time to esophagectomy days (mean)
Akiyama et al., 1998, Japan [35]	Ret	GIC	54	59.6	46	nr	22	Angio	LGA. RGA. SA	14
		C	25	63.8	22	nr	6			
Berrisford et al., 2009, UK [36]	Ret	GIC	22	69 (42–83)	nr	nr	nr	Lap	LGA	14
		C	55	69 (42–83)	nr	nr	nr			
Perry et al., 2010, USA [37]	Ret	GIC	7	nr	nr	nr	2	Lap	LGA. SGV	8–196
		C	25	nr	nr	nr	nr			
Schroder et al., 2010, Germany [38]	Ret	GIC	238	61.1 (59.9–62.4)	198	nr	144	Lap	LGA. LGEA	4.5
		C	181	57.8 (56.3–59.3)	151	nr	66			
Diana et al., 2011, Switzerland [39]	Ret	GIC	19	63 (76–50)	14	24 (17–34)	5	Angio	LGA. SA	17
		C	38	64 (46–82)	32	25 (18–33)	11			
Nguyen et al., 2011, USA [40]	Ret	GIC	81	64.3 ± 10.3	66	nr	23	Lap	LGA	6
		C	71	65.2 ± 11.3	52	nr	36			
Wajed et al., 2011, USA [41]	Ret	GIC	67	67 (42–84)	55	26 (18–33)	66	Lap	LGA	14
		C	64	67 (42–84)	53	26 (18–33)	63			
Patel et al., 2016, USA [42]	Ret	GIC	77	61.5 ± 9.6	nr	nr	nr	Lap	NR	7
		C	41	69.4 ± 10.3	nr	nr	nr			
Ghelfi et al., 2017, USA [43]	Ret	GIC	46	63 (57–72)	33	24 (22–27)	31	Angio	LGA. RA. SGV	21
		C	13	62 (60–66)	10	24 (23–28)	5			
Pham et al., 2017, USA [44]	Ret	GIC	21	65 ± 4.8	18	27 ± 4.8	20	Lap	LGA. SGV	121
		C	9	62 ± 6.8	9	31 ± 5.8	5			
Siegal et al., 2018, USA [45]	Ret	GIC	38	64.3 (49.8–79.4)	29	24.0 (18.7–34.3)	36	Lap	LGA. SGV	98
		C	169	65.8 (24.3–82.7)	139	26.5 (15.6–46.0)	121			
Carrott et al., 2019, USA [46]	Ret	GIC	28	nr	nr	nr	nr	Lap	LGA	87 (26–196)
		C	311	nr	nr	nr	nr			
Kohler et al., 2019, Germany [47]	Ret	GIC	14	63 (36–77)	13	nr	14	Lap	LGA. SGV	5 (3–7)
		C	8	68 (52–82)	7	nr	6			
Mils et al., 2022, Spain [48]	RCT	GIC	20	55 (39–77)	19	25.5 (18–36)	19	Angio	LGA. RA. SGV	20
		C	18	61 (44–79)	15	25 (17–41)	17			

Ret retrospective study, *RCT* randomized controlled trial, *Angio* preoperative embolization, *Lap* laparoscopic ischemic conditioning, *LGA* left gastric artery, *RGA* right gastric artery, *SA* splenic artery, *SGV* short gastric vessels, *LGEA* left gastroepiploic artery nr not reported

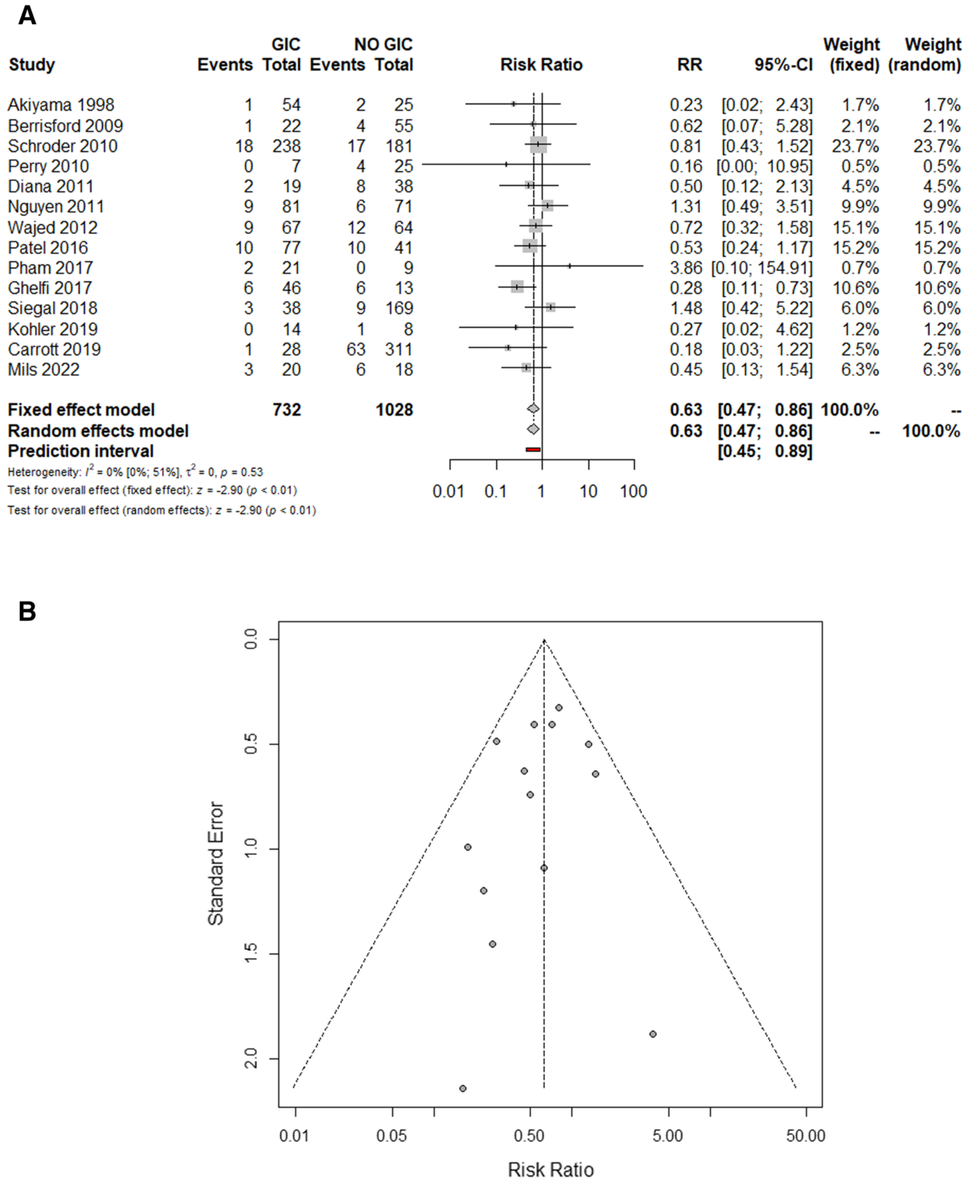

Fig. 2 Anastomotic leak. Forrest (**A**) and Funnel (**B**) plot. *RR* risk ratio, *95% CI* confidence interval

were 0.45 and 0.89, respectively. The heterogeneity was zero ($I^2=0.0\%$, 95% CI 0.0–51%; $p<0.01$) and $\tau^2=0.01$. The Funnel plot (Fig. 2B) and the Egger test ($p=0.49$) did not show evidence of publication bias.

AS was reported in 13 studies (1722 patients). The cumulative incidence of AS was reduced for GIC vs. no GIC (4.8% vs. 18.8%). Compared to no GIC, GIC was associated with a significantly reduced AS risk (RR = 0.51; 95% CI 0.29–0.91; $p=0.02$) (Fig. 3A). The prediction lower and upper limits were 0.16 and 1.63, respectively. The heterogeneity was low ($I^2=20\%$, 95% CI 0.0–58%; $p=0.24$) and $\tau^2=0.18$. The Funnel plot (Fig. 3B) and the Egger test ($p=0.04$) showed that publication bias could not be excluded.

GCN was reported in 11 studies (1271 patients). The cumulative incidence of GCN was reduced for GIC vs. no GIC (0.2% vs. 1.9%). No differences were found for GIC vs. no GIC (RR = 0.56; 95% CI 0.19–1.61; $p=0.28$) (Fig. 4A). The prediction lower and upper limits were 0.16 and 1.90, respectively. The heterogeneity was zero ($I^2=0.0\%$, 95% CI 0.0–0.0%; $p=1.00$) and $\tau^2=0.0$. The Funnel plot (Fig. 4B) and the Egger test ($p=0.04$) showed that publication bias could not be excluded. For all primary outcomes, the sensitivity analysis showed the robustness of findings in terms of point estimation, relative confidence intervals, and heterogeneity.

Meta-analysis—secondary outcomes

Pulmonary complications (RR = 1.09; 95% CI 0.83–1.44; $p=0.99$; $I^2=0.0\%$), overall complications (RR = 0.87; 95% CI 0.73–1.04; $p=0.19$; $I^2=28\%$), OT (SMD −0.58; 95% CI −1.12, 0.03; $p=0.07$; $I^2=78\%$), ICU length of stay (SMD

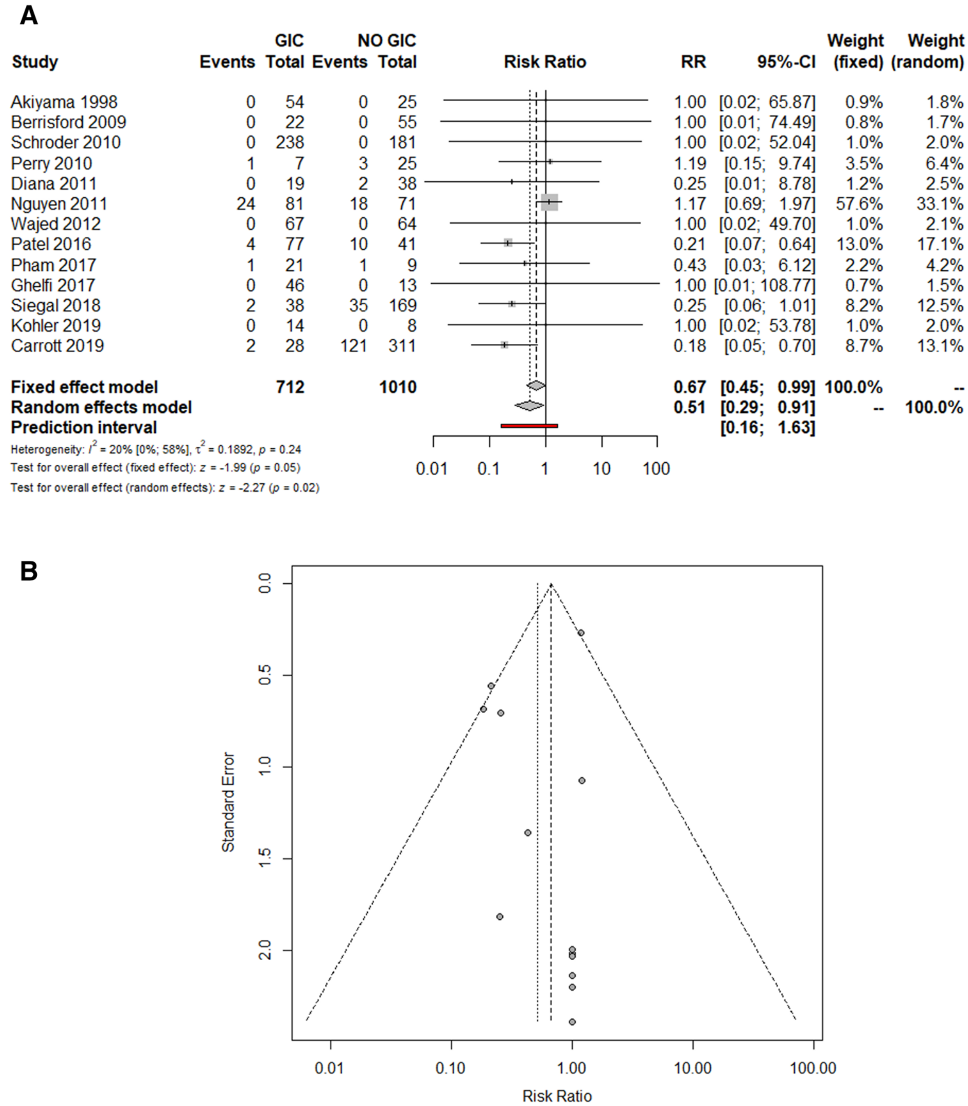

Fig. 3 Anastomotic stricture. Forrest (**A**) and Funnel (**B**) plot. *RR* risk ratio, *95% CI* confidence interval

−0.76; 95% CI −2.15, 0.63; $p=0.29$; $I^2=93\%$), HLOS (SMD 0.66; 95% CI −0.10, 1.43; $p=0.09$; $I^2=90\%$), and 30-day mortality (RR = 0.69; 95% CI 0.38–1.25; $p=0.22$; $I^2=0.0\%$) were similar for GIC vs. no GIC. Using the GRADE tool, we rated the quality of evidence supporting each outcome as low-moderate mainly because of limitations in study design (Supplementary Table 2).

Discussion

This study shows that GIC prior to esophagectomy seems to be associated with a reduced RR of AL and AS with a trend toward a reduced risk for GCN. Pulmonary complications, overall complications OT, ICU length of stay, HLOS, and 30-day mortality seem similar between treatments.

The esophagogastric anastomosis is the most challenging part of esophagectomy and severe related complications such as AL and AS have been described. Factors that potentially contribute to anastomotic failure are tension, technique, malnutrition, patient comorbidities, and inadequate blood supply of the gastric conduit [49, 50]. Patients' vascular status assessed by amount of calcifications in the thoracic aorta or stenosis of the celiac axis may represent an objective risk factor for post-esophagectomy AL. Therefore, optimization of gastric conduit perfusion and maintenance of an efficient submucosal vascular network at the anastomotic site is desirable. Physiologic gastric perfusion is supported by large capillaries, distributed perpendicular to both gastric curvatures, and by small capillary branches that run parallel to both curvatures thus forming a complex vascular network [51]. Ligation of the left gastric artery, left gastroepiploic artery, and short gastric vessels determine a rearrangement of this pattern. Therefore, perfusion dynamics in the gastric conduit occur through the right gastroepiploic artery at the greater curvature, while the tip of the conduit relies on small

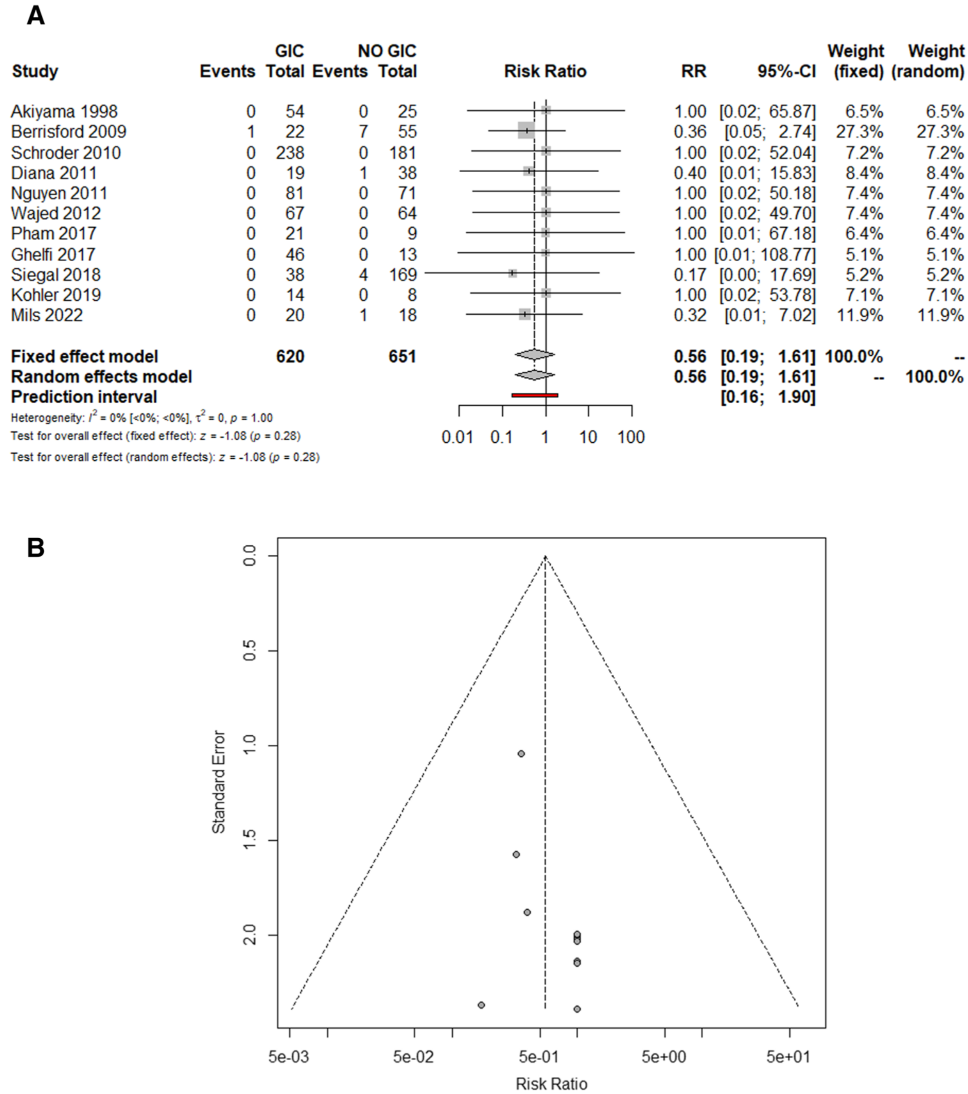

Fig. 4 Gastric conduit necrosis. Forrest (**A**) and Funnel (**B**) plot. *RR* risk ratio, *95% CI* confidence interval

longitudinally oriented collateral connections. Occasionally, this vascular arcade may be prematurely interrupted. The knowledge of these anatomical key points is crucial for the construction of the gastric conduit to prevent ischemia at the anastomotic site [52]. With this aim, GIC prior to esophagectomy has been proposed to allow progressive vascular adaptation and consequent improvement of the submucosal vascular network of the gastric substitute [38–48].

We found that GIC is associated with a significantly reduced RR for AL compared to no GIC. The related heterogeneity was 0.0%. Jogiat et al. [20] also reported reduced odds for AL after ischemic conditioning (OR = 0.67; $p = 0.03$), whereas Kamarajah et al. [18] did not show any difference between GIC and no GIC (OR = 0.79; $p = 0.3$). Furthermore, GIC has been suggested to be associated with a tendency toward minimized leak severity and less need for redo surgery in case of leak occurrence. Specifically, Heger et al. [17] found that AL after GIC tended to be less severe and more likely managed conservatively or with endoscopic stenting, thus reducing the risk for reintervention (25% vs. 69%). Also, Schroder et al. [38] concluded that GIC led to more endoscopic stenting in case of AL rather than reintervention. Similarly, GIC was associated with a significantly reduced risk for AS. The related heterogeneity was low ($I^2 = 20\%$). Our result is different from what reported by Kamarajah et al. (OR = 0.74; $p = 0.5$), and Heger and colleagues [17] (OR = 1.1; $p = 0.76$), who concluded that there were no differences in terms of AS but is similar to what reported by Jogiat et al. [20] who supported reduced odds for AS (OR = 0.48; $p = 0.005$) in favor of GIC. The likely explanation for a reduced AL is a better vascular/oxygen supply to the anastomotic site induced by preoperative GIC. This is indirectly supported by previous studies using Doppler flowmetry, fluorescence microscopy, hyperspectral imaging, and angiography [7, 12, 13, 53]. Histological changes with neoangiogenesis, increased microvessels count, and vessel hypertrophy have also been reported [44]. Similarly, a possible explanation for reduced AS may be an increased preservation of the muscularis propria layer and decreased collagen deposition, with reduced fibrosis at the anastomotic site [19]. Despite the low heterogeneity, our results should be carefully interpreted, because the potential effect of confounders associated with an increased risk for AL and AS such as anastomosis location (thoracic vs. cervical), anastomotic technique (linear vs. circular stapled, omental wrapping), timing of GIC (<14 days vs. >14 days), technique of GIC (single vs. multi-vessel GIC, and laparoscopy vs. embolization), blood flow assessment with indocyanine green, patient age and comorbidities, steroid use, patient body morphometrics, past medical history, intraoperative interventions (i.e. blood transfusion, intraoperative hypotension, etc.), different anaesthesia protocols, neoadjuvant treatment, and tumor characteristics (i.e. grading, size, location, R0 status) [49]. Finally, despite the lack of statistical significance, a trend toward clinically reduced risk for GCN was observed for preoperative GIC. This is similar to what reported by Kamarajah and colleagues [18] who found a significantly reduced risk for conduit necrosis after ischemic conditioning ($OR=0.29$; $p=0.013$). Looking at secondary outcomes, no differences were noted for pulmonary complications, overall complications, OT, ICU length of stay, HLOS, and 30-day mortality.

Almost 80% of included patients in our study underwent laparoscopic GIC. Possible disadvantages of this approach are increased difficulty in dissection and lymphadenectomy at the time of esophagectomy because of adhesions. Also, use of staplers for en bloc ligation of the left gastric artery pedicle may be associated with significant scarring around the staple line. Furthermore, laparoscopic GIC represents a supplementary surgical intervention with increased costs, risk for GIC-related complications (i.e., bleeding requiring transfusions), and need for general anaesthesia. There is also risk of arterial injury and conversion to open, but this has not yet been described. In contrast, GIC via embolization may be regarded as a less invasive technique, although splenic infarction/necrosis, necrotizing cholecystitis, distal pancreatitis, and bleeding at the femoral access have been labeled [10, 35, 54, 55]. To date, a precise incidence of complications following both surgical and radiological GIC cannot be outlined, because the majority of enrolled articles are focused on the clinical advantage that GIC may have on the esophagogastric anastomosis during esophagectomy. Besides, further studies looking at the cost-analysis of GIC are needed.

There are sparse data describing the optimal timing between GIC and esophagectomy. It has been theorized that waiting >2 weeks may be associated with better outcomes compared to a shorter period (<2 weeks) [19]. Hypothetically, waiting longer intervals may be associated with improved neoangiogenesis. Furthermore, it remains unclear which vessels must be ligated to allow an adequate fundic revascularization [20]. Some authors advocate dividing only the left gastric artery while other suggested a multi-vessel approach. Unfortunately, a formal quantitative analysis to assess the ideal timing between GIC and esophagectomy and the potential benefits of a multi-vessel approach was not feasible. Opponents of GIC may argue that longer overall operative times, increased risk for GIC-related morbidity, and increased health-care costs combined with limited advantages do not justify the utilization of this strategy. Therefore, it should be considered that the reduced AL and AS risk may mitigate the initial expenses with ultimate global cost effectiveness. Furthermore, not all the patients probably will benefit from GIC prior to esophagectomy, but it is likely that some high-risk individuals could be good candidates [56– 58]. More specifically, patients with poor preoperative vascular status, major calcification of the thoracic aorta, and stenosis of the celiac axis could hypothetically benefit from GIC before esophagectomy [58].

Notably, both AL and AS may be also influenced by surgeon proficiency, learning curves, structured training/mentorship programs and hospital volumes [59–61]. It has been shown that case-load centralization in high-volume centres significantly reduce mortality and may improve outcomes [62]. Based on these considerations, it should be considered that AL and AS may not entirely reflect the effect of preoperative GIC but are also influenced by surgeon experience. Finally, the introduction of new technologies such as fluorescence imaging with indocyanine green to assess the gastric conduit perfusion/anastomosis may hypothetically further improve outcomes.

Our study suffers from the typical limitations of a meta-analysis including observational studies, i.e., lack of inclusion criteria defined a priori, lack of homogenous surgical approach, and lack of globally defined postoperative management protocols. Second, AL and AS were not uniformly defined and classified among included studies. Third, the different techniques for GIC (laparoscopy vs. embolization), number of sealed vessels, and timing prior to esophagectomy were diverse and may potentially affect outcomes. Fourth, surgeon experience and volume were not measured with a potential bias and influence on outcomes. Lastly, the effect of GIC in the setting of neoadjuvant treatments (CROSS vs. FLOT) in locally advanced disease is still unclear and need to be defined. Specifically, GIC may be accomplished during staging laparoscopy prior neoadjuvant treatment therefore the interval time for resection may be delayed up to 5–7 weeks after the end of treatment while delivery of chemotherapeutic agents to junctional tumors after ischemic conditioning is unknown.

Conclusions

GIC prior to esophagectomy seems associated with a reduced risk for AL and AS. Further studies are necessary to identify the subset of patients who can benefit from this procedure, the optimal technique, and the timing of GIC prior to esophagectomy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13304-023-01601-9.

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Declarations

Conflict of interest All authors have no conflicts of interest or financial ties to disclose.

Research involving human participants and/or animals, and Informed consent Not applicable.

References

1. Kutup A, Nentwich MF, Bollschweiler E, Bogoevski D, Izbicki JR, Hölscher AH (2014) What should be the gold standard for the surgical component in the treatment of locally advanced esophageal cancer: transthoracic versus transhiatal esophagectomy. Ann Surg 260(6):1016–1022. https://doi.org/10.1097/SLA.0000000000000335
2. McCulloch P, Ward J, Tekkis PP, ASCOT group of surgeons; British Oesophago-Gastric Cancer Group (2003) Mortality and morbidity in gastro-oesophageal cancer surgery: initial results of ASCOT multicentre prospective cohort study. BMJ 327(7425):1192–1197. https://doi.org/10.1136/bmj.327.7425.1192
3. Aiolfi A, Sozzi A, Bonitta G, Lombardo F, Cavalli M, Cirri S, Campanelli G, Danelli P, Bona D (2022) Linear- versus circular-stapled esophagogastric anastomosis during esophagectomy: systematic review and meta-analysis. Langenbecks Arch Surg 407(8):3297–3309. https://doi.org/10.1007/s00423-022-02706-2
4. Goense L, Meziani J, Ruurda JP, van Hillegersberg R (2019) Impact of postoperative complications on outcomes after oesophagectomy for cancer. Br J Surg 106(1):111–119. https://doi.org/10.1002/bjs.11000
5. Markar S, Gronnier C, Duhamel A, Mabrut JY, Bail JP, Carrere N, Lefevre JH, Brigand C, Vaillant JC, Adham M, Msika S, Demartines N, Nakadi IE, Meunier B, Collet D, Mariette C, FREGAT (French Eso-Gastric Tumors) Working Group, FRENCH (Fédération de Recherche EN CHirurgie), and AFC (Association Française de Chirurgie) (2015) The impact of severe anastomotic leak on long-term survival and cancer recurrence after surgical resection for esophageal malignancy. Ann Surg 262(6):972–980. https://doi.org/10.1097/SLA.0000000000001011
6. Shiraishi O, Yasuda T, Kato H, Momose K, Hiraki Y, Yasuda A, Shinkai M, Imano M (2022) Circular stapler method for avoiding stricture of cervical esophagogastric anastomosis. J Gastrointest Surg 26(4):725–732. https://doi.org/10.1007/s11605-022-05266-4
7. Urschel JD (1995) Ischemic conditioning of the rat stomach: implications for esophageal replacement with stomach. J Cardiovasc Surg (Torino) 36(2):191–193
8. Hölscher AH, Schneider PM, Gutschow C, Schröder W (2007) Laparoscopic ischemic conditioning of the stomach for esophageal replacement. Ann Surg 245(2):241–246. https://doi.org/10.1097/01.sla.0000245847.40779.10
9. Veeramootoo D, Shore AC, Shields B, Krishnadas R, Cooper M, Berrisford RG, Wajed SA (2010) Ischemic conditioning shows a time-dependant influence on the fate of the gastric conduit after minimally invasive esophagectomy. Surg Endosc 24(5):1126–1131. https://doi.org/10.1007/s00464-009-0739-1
10. Mingol-Navarro F, Ballester-Pla N, Jimenez-Rosellon R (2019) Ischaemic conditioning of the stomach previous to esophageal surgery. J Thorac Dis 11(Suppl 5):S663–S674. https://doi.org/10.21037/jtd.2019.01.43
11. Alfabet C, Montero EF, Paes Leme LF, Higashi VS, Sallum Fo CF, Fagundes DJ, Gomes PO (2003) Progressive gastric perfusion in rats: role of ischemic conditioning. Microsurgery 23(5):513–516. https://doi.org/10.1002/micr.10164
12. Reavis KM, Chang EY, Hunter JG, Jobe BA (2005) Utilization of the delay phenomenon improves blood flow and reduces collagen deposition in esophagogastric anastomoses. Ann Surg 241(5):736–457. https://doi.org/10.1097/01.sla.0000160704.50657.32. (**discussion 745-7**)
13. Lamas S, Azuara D, de Oca J, Sans M, Farran L, Alba E, Escalante E, Rafecas A (2008) Time course of necrosis/apoptosis and neovascularization during experimental gastric conditioning. Dis Esophagus 21(4):370–376. https://doi.org/10.1111/j.1442-2050.2007.00772.x
14. Yetasook AK, Leung D, Howington JA et al (2013) Laparoscopic ischemic conditioning of the stomach prior to esophagectomy. Dis Esophagus 26:479–486
15. Farran L, Miro M, Alba E et al (2011) Preoperative gastric conditioning in cervical gastroplasty. Dis Esophagus 24:205–210
16. Zahedi M, Ganai S, Yetasook AK et al (2012) Tu1767 Laparoscopic ischemic conditioning as a modality to reduce gastric conduit morbidity following esophagectomy. Gastroenterology 142:S-1094

17. Heger P, Blank S, Diener MK, Ulrich A, Schmidt T, Büchler MW, Mihaljevic AL (2017) Gastric preconditioning in advance of esophageal resection-systematic review and meta-analysis. J Gastrointest Surg 21(9):1523–1532. https://doi.org/10.1007/s11605-017-3416-z
18. Kamarajah SK, Boyle C, Bundred JR, Tan BH (2020) Critical appraisal of gastric conduit ischaemic conditioning (GIC) prior to oesophagectomy: a systematic review and meta-analysis. Int J Surg 77:77–82. https://doi.org/10.1016/j.ijsu.2020.03.020
19. Michalinos A, Antoniou SA, Ntourakis D, Schizas D, Ekmektzoglou K, Angouridis A, Johnson EO (2020) Gastric ischemic preconditioning may reduce the incidence and severity of anastomotic leakage after oesophagectomy: a systematic review and meta-analysis. Dis Esophagus 33(10):doaa010. https://doi.org/10.1093/dote/doaa010
20. Jogiat UM, Sun WYL, Dang JT, Mocanu V, Kung JY, Karmali S, Turner SR, Switzer NJ (2022) Gastric ischemic conditioning prior to esophagectomy reduces anastomotic leaks and strictures: a systematic review and meta-analysis. Surg Endosc 36(7):5398–5407. https://doi.org/10.1007/s00464-021-08866-4
21. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 339:b2700. https://doi.org/10.1136/bmj.b2700
22. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. JAMA 283(15):2008–2012. https://doi.org/10.1001/jama.283.15.2008
23. Goossen K, Tenckhoff S, Probst P, Grummich K, Mihaljevic AL, Büchler MW, Diener MK (2018) Optimal literature search for systematic reviews in surgery. Langenbecks Arch Surg 403(1):119–129. https://doi.org/10.1007/s00423-017-1646-x
24. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JP (2016) ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355:i4919. https://doi.org/10.1136/bmj.i4919
25. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA, Cochrane Bias Methods Group; Cochrane Statistical Methods Group (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 18(343):d5928. https://doi.org/10.1136/bmj.d5928
26. Guyatt GH, Oxman AD, Vist GE et al (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336(7650):924–926
27. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7(3):177–188
28. Aiolfi A, Bona D, Guerrazzi G, Bonitta G, Rausa E, Panizzo V, Campanelli G, Micheletto G (2020) Intracorporeal versus extracorporeal anastomosis in laparoscopic right colectomy: an updated systematic review and cumulative meta-Analysis. J Laparoendosc Adv Surg Tech A 30(4):402–412. https://doi.org/10.1089/lap.2019.0693
29. Borenstein M, Hedges LV, Higgins JP, Rothstein HR (2010) A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 1(2):97–111
30. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327:557–560
31. Aiolfi A, Tornese S, Bonitta G et al (2019) Roux-en-Y gastric bypass: systematic review and Bayesian network meta-analysis comparing open, laparoscopic, and robotic approach. Surg Obes Relat Dis 15(6):985–994
32. Alberto, Aiolfi Francesca, Lombardo Gianluca, Bonitta Piergiorgio, Danelli Davide, Bona (2021) Systematic review and updated network meta-analysis comparing open laparoscopic and robotic pancreaticoduodenectomy Abstract Updates in Surgery 73(3) 909-922 10.1007/s13304-020-00916-1
33. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21(11):1539–1558
34. R Development Core Team (2015) A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna
35. Akiyama S, Ito S, Sekiguchi H, Fujiwara M, Sakamoto J, Kondo K, Kasai Y, Ito K, Takagi H (1996) Preoperative embolization of gastric arteries for esophageal cancer. Surgery 120(3):542–546. https://doi.org/10.1016/s0039-6060(96)80075-4
36. Berrisford RG, Veeramootoo D, Parameswaran R, Krishnadas R, Wajed SA (2009) Laparoscopic ischaemic conditioning of the stomach may reduce gastric-conduit morbidity following total minimally invasive oesophagectomy. Eur J Cardiothorac Surg 36(5):888–893. https://doi.org/10.1016/j.ejcts.2009.01.055. (**discussion 893**)
37. Perry KA, Enestvedt CK, Pham TH, Dolan JP, Hunter JG (2010) Esophageal replacement following gastric devascularization is safe, feasible, and may decrease anastomotic complications. J Gastrointest Surg 14(7):1069–1073. https://doi.org/10.1007/s11605-010-1204-0
38. Schröder W, Hölscher AH, Bludau M, Vallböhmer D, Bollschweiler E, Gutschow C (2010) Ivor-Lewis esophagectomy with and without laparoscopic conditioning of the gastric conduit. World J Surg 34(4):738–743. https://doi.org/10.1007/s00268-010-0403-x
39. Diana M, Hübner M, Vuilleumier H, Bize P, Denys A, Demartines N, Schäfer M (2011) Redistribution of gastric blood flow by embolization of gastric arteries before esophagectomy. Ann Thorac Surg 91(5):1546–1551. https://doi.org/10.1016/j.athoracsur.2011.01.081
40. Nguyen NT, Nguyen XM, Reavis KM, Elliott C, Masoomi H, Stamos MJ (2012) Minimally invasive esophagectomy with and without gastric ischemic conditioning. Surg Endosc 26(6):1637–1641. https://doi.org/10.1007/s00464-011-2083-5
41. Wajed SA, Veeramootoo D, Shore AC (2012) Video. Surgical optimisation of the gastric conduit for minimally invasive oesophagectomy. Surg Endosc 26(1):271–276. https://doi.org/10.1007/s00464-011-1855-2
42. Patel LY, Ganai S, Johnson B et al (2016) Clinical outcomes following esophagectomy with and without laparoscopic ischemic gastric pre-conditioning. Gastroenterology 150:S1181–S1182
43. Ghelfi J, Brichon PY, Frandon J, Boussat B, Bricault I, Ferretti G, Guigard S, Sengel C (2017) Ischemic gastric conditioning by preoperative arterial embolization before oncologic esophagectomy: a single-center experience. Cardiovasc Intervent Radiol 40(5):712–720. https://doi.org/10.1007/s00270-016-1556-2
44. Pham TH, Melton SD, McLaren PJ, Mokdad AA, Huerta S, Wang DH, Perry KA, Hardaker HL, Dolan JP (2017) Laparoscopic ischemic conditioning of the stomach increases neovascularization of the gastric conduit in patients undergoing esophagectomy for cancer. J Surg Oncol 116(3):391–397. https://doi.org/10.1002/jso.24668
45. Siegal SR, Parmar AD, Haisley KR, Tieu BH, Schipper PH, Hunter JG, Dolan JP (2018) Gastric ischemic conditioning prior to esophagectomy is associated with decreased stricture

rate and overall anastomotic complications. J Gastrointest Surg 22(9):1501–1507. https://doi.org/10.1007/s11605-018-3817-7
46. Carrott PW, Miller JRN, Chang A, Reddy R, Lin J, Lagisetty KH (2019) Gastric ischemic conditioning before esophagectomy: timing and method matter. J Am Coll Surg 229(4):e207–e208. https://doi.org/10.1016/j.jamcollsurg.2019.08.1430
47. Köhler H, Jansen-Winkeln B, Maktabi M, Barberio M, Takoh J, Holfert N, Moulla Y, Niebisch S, Diana M, Neumuth T, Rabe SM, Chalopin C, Melzer A, Gockel I (2019) Evaluation of hyperspectral imaging (HSI) for the measurement of ischemic conditioning effects of the gastric conduit during esophagectomy. Surg Endosc 33(11):3775–3782. https://doi.org/10.1007/s00464-019-06675-4
48. Mils K, Miró M, Farran L, Videla S, Alba E, Estremiana F, Bettonica C, Aranda H (2022) A pilot randomized controlled trial on the utility of gastric conditioning in the prevention of esophagogastric anastomotic leak after Ivor Lewis esophagectomy. The APIL_2013 trial. Int J Surg 106:106921. https://doi.org/10.1016/j.ijsu.2022.106921
49. Kamarajah SK, Lin A, Tharmaraja T, Bharwada Y, Bundred JR, Nepogodiev D, Evans RPT, Singh P, Griffiths EA (2020) Risk factors and outcomes associated with anastomotic leaks following esophagectomy: a systematic review and meta-analysis. Dis Esophagus 33(3):doz089
50. Nickel F, Studier-Fischer A, Özdemir B et al (2021) Optimization of anastomotic technique and gastric conduit perfusion with hyperspectral imaging in an experimental model for minimally invasive esophagectomy. European J Surg Oncol. https://doi.org/10.1101/2021.10.03.462901
51. Markar SR, Arya S, Karthikesalingam A et al (2013) Technical factors that affect anastomotic integrity following esophagectomy: systematic review and meta-analysis. Ann Surg Oncol 20:4274–4281
52. Zehetner J, DeMeester SR, Alicuben ET et al (2015) Intraoperative assessment of perfusion of the gastric graft and correlation with anastomotic leaks after esophagectomy. Ann Surg 262:74–78
53. Beck SM, Malay MB, Gagné DJ et al (2011) Experimental model of laparoscopic gastric ischemic preconditioning prior to transhiatal esophagectomy. Surg Endosc 25:2470–2477
54. Ney A, Kumar R (2014) Does preoperative ischaemic conditioning with gastric vessel ligation reduce anastomotic leaks in oesophagectomy? Interact Cardiovasc Thorac Surg 19:121–124
55. Kechagias A, Van Rossum PS, Ruurda JP et al (2016) Ischemic conditioning of the stomach in the prevention of esophagogastric anastomotic leakage after esophagectomy. Ann Thorac Surg 101:1614–1623
56. van Rossum PS, Haverkamp L, Verkooijen HM et al (2015) Calcification of arteries supplying the gastric tube: a new risk factor for anastomotic leakage after esophageal surgery. Radiology 274:124–132
57. Tzortzakakis A, Kalarakis G, Huang B, Terezaki E, Koltsakis E, Kechagias A, Tsekrekos A, Rouvelas I (2022) Role of radiology in the preoperative detection of arterial calcification and celiac trunk stenosis and its association with anastomotic leakage post esophagectomy, an up-to-date review of the literature. Cancers (Basel) 14(4):1016. https://doi.org/10.3390/cancers14041016
58. de Groot E, Schiffmann LM, van der Veen A, Borggreve A, de Jong P, Dos Santos DP, Babic B, Fuchs H, Ruurda J, Bruns C, van Hillegersberg R, Schröder W (2023) Laparoscopic ischemic conditioning prior esophagectomy in selected patients: the ISCON trial. Dis Esophagus. https://doi.org/10.1093/dote/doad027. (**Epub ahead of print**)
59. van Workum F, Stenstra MHBC, Berkelmans GHK et al (2019) Learning curve and associated morbidity of minimally invasive esophagectomy: a retrospective multicenter study. Ann Surg 269:88–94
60. Markar SR, Mackenzie H, Lagergren P, Hanna GB, Lagergren J (2016) Surgical proficiency gain and survival after esophagectomy for cancer. J Clin Oncol 34(13):1528–1536
61. Halliday LJ, Doran SLF, Sgromo B et al (2020) Variation in esophageal anastomosis technique—the role of collaborative learning. Dis Esophagus 33:doz072
62. Tapias LF, Morse CR (2014) Minimally invasive Ivor Lewis esophagectomy: description of a learning curve. J Am Coll Surg 218(6):1130–1140