Surgical Endoscopy (2022) 36:5398–5407
https://doi.org/10.1007/s00464-021-08866-4

**2021 SAGES ORAL**

# Gastric ischemic conditioning prior to esophagectomy reduces anastomotic leaks and strictures: a systematic review and meta-analysis

**Uzair M. Jogiat[1] · Warren Y. L. Sun[1] · Jerry T. Dang[1] · Valentin Mocanu[1] · Janice Y. Kung[2] · Shahzeer Karmali[1] · Simon R. Turner[3] · Noah J. Switzer[1,4]**

Received: 15 June 2021 / Accepted: 1 November 2021 / Published online: 15 November 2021

## Abstract

**Background** Gastric ischemic conditioning (GIC) is a strategy to promote neovascularization of the gastric conduit to reduce the risk of anastomotic complications following esophagectomy. Despite a number of studies and reviews published on the concept of ischemic conditioning, there remains no clear consensus regarding its utility. We performed an updated systematic review and meta-analysis to determine the impact of GIC, particularly on anastomotic leaks, conduit ischemia, and strictures.

**Methods** A systematic search of MEDLINE, EMBASE, Scopus, Web of Science, and Cochrane Library was performed on February 5th, 2020 by a university librarian after selection of key search terms with the research team. Inclusion criteria included human participants undergoing esophagectomy with gastric conduit reconstruction, age $\geq 18$, $N \geq 5$, and GIC performed prior to esophagectomy. Our primary outcome of interest was anastomotic leaks. Our secondary outcome was gastric conduit ischemia, anastomotic strictures, and overall survival. Meta-analysis was performed with RevMan 5.4.1 using a Mantel–Haenszel fixed-effects model.

**Results** A total of 1712 preliminary studies were identified and 23 studies included for final review. GIC was performed in 1178 (53.5%) patients. Meta-analysis revealed reduced odds of anastomotic leaks (OR 0.67; 95% CI 0.46–0.97; $I^2 = 5\%$; $p = 0.03$) and anastomotic strictures (OR 0.48; 95% CI 0.29–0.80; $I^2 = 65\%$; $p = 0.005$). Meta-analysis revealed no difference in odds of conduit ischemia (OR 0.40; 95% CI 0.13–1.23; $I^2 = 0\%$; $p = 0.11$) and no difference in odds of overall survival (OR 0.54; 95% CI 0.29–1.02; $I^2 = 22\%$; $p = 0.06$).

**Conclusion** GIC is associated with reduced odds of anastomotic leaks and anastomotic strictures and may decrease morbidity in patients undergoing esophagectomy. Further prospective randomized trials are needed to better identify the optimal patient population, timing, and techniques used to best achieve GIC.

**Keywords** Gastric ischemic conditioning · Esophagectomy · Anastomotic leaks

Anastomotic leaks after esophagectomy are associated with an increased mortality, prolonged hospital stay, and have been demonstrated to lower overall and progression-free survival [1]. Despite advancement in operative technique and perioperative care, the incidence of anastomotic leaks remains high and ranges from 10 to 40% [2–4]. Ischemia to the gastric conduit is thought to play a pivotal role in the etiology of anastomotic leaks, but strategies to overcome this problem remain elusive.

In animal trials published two decades ago, partial devascularization of the stomach improved perfusion of the proximal stomach [5]. Evidence from these trials informed future studies which investigated the effect of this form of gastric ischemic conditioning (GIC) in humans [6]. The general

---

✉ Noah J. Switzer
nswitzer@ualberta.ca

[1] Division of General Surgery, Department of Surgery, University of Alberta, Edmonton, Canada

[2] John W. Scott Health Sciences Library, University of Alberta, Edmonton, Canada

[3] Division of Thoracic Surgery, Department of Surgery, University of Alberta, Edmonton, Canada

[4] Division of General Surgery, Department of Surgery, Royal Alexandra Hospital, Room 415 Community Services Center, 10240 Kingsway Avenue, Edmonton, AB T5H3V9, Canada

approach involves selective ligation of the blood supply to the stomach, namely the left gastric and short gastric arteries, either through embolization or surgery, with preservation of the right gastroepiploic artery, followed by an interval esophagectomy.

Proponents of GIC have previously reported the positive results on anastomotic leak rates from the retrospective data evidenced in this review. However, there are notable drawbacks that have been raised among the literature. A surgical ligation may incur its own complications and could increase the difficulty of subsequent esophagectomy by generating post-operative adhesions. At the time of resection, posterior dissection and lymphadenectomy may be more challenging which could compromise the overall quality of the oncologic resection. Ischemic conditioning through angiographic means is also not without risk, and there have been reports of splenic infarction and pancreatitis [6, 7]. Currently, there remains no consensus on the type of ischemic conditioning, the duration of delay prior to esophagectomy, or the potential benefit of the intervention [7–10].

The aim of our present work was to conduct a systematic review to evaluate the current literature on GIC, with our primary outcome serving as incidence of anastomotic leaks and our secondary outcomes being strictures, ischemia, and overall survival.

## Materials and methods

### Search strategy

This systematic review was conducted with adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A systematic search of MEDLINE, EMBASE, Scopus, Web of Science, and Cochrane Library was performed on February 5th, 2020 by a university librarian (JK) after selection of key terms with the research team. The searches included a combination of free text and controlled vocabulary terms related to ischemic conditioning and esophagectomies. Search terms included “Ischemic Preconditioning OR [variations of the terms]” AND “Esophagectomy OR [variations of the term]” (Supplementary Table 1). In addition to finding literature in bibliographic databases, the research team also reviewed the first 200 results in Google Scholar and the bibliography lists of included studies. A search of bibliographies in seven of the current systematic reviews on the topic was also performed to ensure no studies were overlooked.

### Inclusion and exclusion criteria

Inclusion criteria included human participants undergoing esophagectomy with gastric conduit reconstruction, age $\geq 18$, greater than five patients, GIC (any method) performed prior to esophagectomy, and studies published in English. Exclusion criteria included conference abstracts with insufficient data, duplicate studies, and case reports. One primary researcher evaluated titles and abstracts (UJ), with potentially eligible studies undergoing a full-text review by two primary researchers (UJ, WS). Disagreement in study inclusion or exclusion criteria between the two primary researchers was resolved by consensus.

### Data extraction

For studies meeting inclusion criteria, two primary researchers (UJ, WS) extracted data on study characteristics. These included author, year of publication, study design, $n$ value for ischemic conditioning, n value for control (if applicable), mean baseline patient demographics, method of GIC, time to GIC, and the aforementioned study outcomes. Baseline patient characteristics included age, sex, indication for surgery, neoadjuvant therapy status, and smoking status. Oncologic data extracted included type of cancer, stage of cancer, and location of cancer (proximal, middle, distal). Comparison of pooled data of all studies included in the review are provided in Supplementary Tables 4–6.

### Study outcomes

The aim of our study was to determine the impact of GIC on post-operative complications, such as anastomotic leaks, strictures, and ischemia. The primary outcome measure was incidence of anastomotic leaks. The secondary outcome measures were gastric conduit ischemia, anastomotic strictures, and overall survival.

### Assessment of methodological quality

Methodological quality of studies was assessed by two independent reviewers (UJ, WS). Methodological quality was formally assessed using the methodological index for non-randomized studies (MINORS) criteria for non-randomized trials. MINORS is an externally validated 12 item index utilized to assess the methodological quality of comparative and non-comparative cohort studies [11].

### Statistical analysis

Descriptive categorical data were expressed as percentages and continuous data were expressed as weighted means where appropriate. Where medians were reported, values were converted to means using the method reported by Hozo et al. [12] Meta-analysis was conducted to evaluate differences in anastomotic leaks, anastomotic strictures, conduit ischemia, and overall survival for patients receiving GIC compared to those receiving standard of care. Where direct comparisons and meta-analysis could not be conducted, pooled proportions were used to describe outcomes. Estimated effects were calculated using RevMan 5.4.1 software with a Mantel–Haenszel fixed-effects model. Heterogeneity was quantified by the $I^2$ statistic: (1) low = 25%; (2) moderate = 50%; and (3) high = 75%. Tests for statistical significance were two-tailed with significant p-values defined as $< 0.05$. Statistical analysis of pooled data was not performed given lack of comparator groups, and results are provided for gross comparison.

## Results

### Study selection

A total of 1712 results were retrieved and 1071 unique records remained for the title and abstract screening phase (Fig. 1). Of the abstracts meeting the initial screening criteria, 1008 were excluded either because they did not meet the formal inclusion criteria or met exclusion criteria for our study. This resulted in 63 studies undergoing full-text assessment for eligibility. A total of 23 studies met inclusion criteria, 21 of which were full-text articles and two of which were conference abstracts. Of the included manuscripts, 14 were retrospective studies and 9 were prospective. Two studies from the same institution met inclusion criteria given the significant lapse in time between the studies and lack of

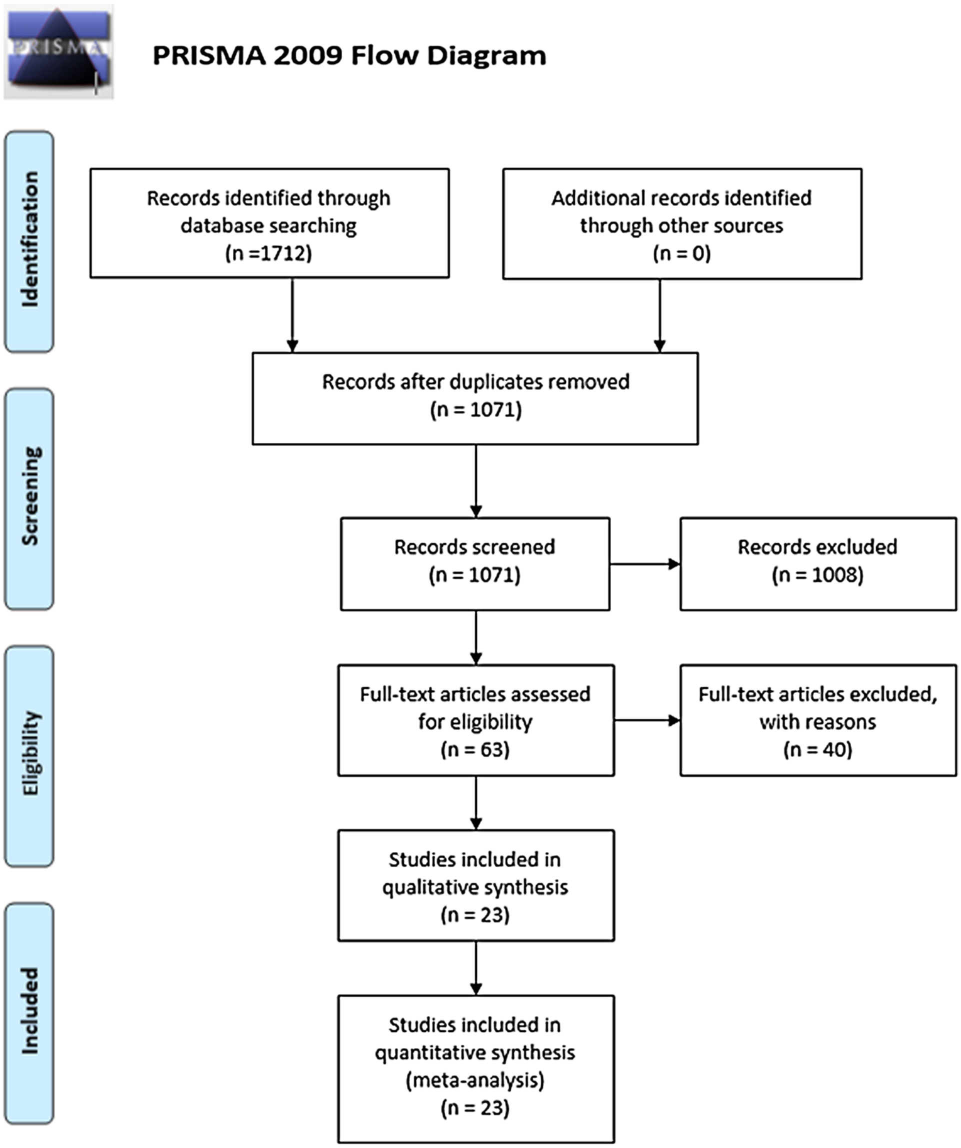


**Fig. 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of included studies

significant overlap in the sample sizes [13, 14]. No major methodological flaws were identified, and the results of the search are provided in the PRISMA flow diagram below (Fig. 1).

## Study characteristics

A total of 2203 patients, the majority of which were male ($n = 1515$, 69.8%) with a mean weighted age of 63 ± 7.1 years, were included (Table 1). GIC was performed in 1178 (53.5%) patients with a mean time from GIC to surgery of 28 days ± 37.3. Of the included studies reporting GIC, 12 were comparator studies and 11 were observational, 17 utilized the laparoscopic method, while 6 utilized embolization (Table 2). Of the studies providing histologic data, there were 842 adenocarcinomas and 371 squamous cell carcinoma patients in the included studies (Supplementary Table 2). The most common stage recorded was stage III, comprising 319 (54%) patients and the most frequent location of tumor reported in studies providing this data were distal, comprising 92 (52%) patients. For those that did include such data, patients who underwent ischemic conditioning generally matched controls. Given the extensive variability and missing data among baseline patient's characteristic data and oncologic data across the included studies, these were not included in the sub-group analysis and are reported in the supplementary tables.

Regarding neoadjuvant therapy, 15 studies contained patients undergoing neoadjuvant therapy prior to ischemic conditioning. Out of these, neoadjuvant chemoradiotherapy was reported in 13 studies. Of the included studies, seven contained data on staging, with stage three being the most common.

Laparoscopic ischemic conditioning was more common than angiographic ischemic conditioning ($n = 1835$ vs. $n = 289$, respectively). In the included studies, there was an equal distribution among patients who underwent ischemic conditioning for less than 7 days compared to those who underwent ischemic conditioning for greater than 7 days ($n = 1059$ vs. $n = 1112$, respectively). More patients underwent ischemic conditioning with two or more vessels ligated as compared to a single vessel ($n = 1333$ vs. $n = 840$, respectively).

## Reduced odds of anastomotic leaks in patients with GIC

Anastomotic leaks were reported in 12 comparative studies, of which 9 reported laparoscopic GIC compared to three reporting angiographic GIC. Meta-analysis revealed a significant reduction in anastomotic leaks in patients undergoing GIC (OR 0.67; 95% CI 0.46–0.97; $I^2 = 5\%$; $p = 0.03$) compared to those undergoing esophagectomy alone (Fig. 2).

**Table 1** Baseline patient characteristics of included studies

| Study | Age, yrs, mean | Male | Indication: cancer | Indication: benign | Neoadjuvant | Smoking status |
|---|---|---|---|---|---|---|
| Akiyama 1998 | 60.9 | 68 | NR | NR | 28 | NR |
| Berrisford 2009 | 69 (med) | 67 | NR | NR | NR | NR |
| Bludau 2012 | 60.9 | 16 | 19 | 0 | 14 | NR |
| Carrott 2019 | 69 (med) | 22 | NR | NR | NR | NR |
| Diana 2011 | 63.7 | 46 | 57 | 0 | 34 | S: 46<br>N: 11 |
| Farran 2010 | 59.8 | 32 | 20 | 19 | NR | NR |
| Ghelfi 2017 | 63 (med) | 43 | 59 | 0 | 36 | NR |
| Holscher 2007 | 61.9 | 68 | 83 | 0 | 42 | NR |
| Isomura 1999 | 59 | 28 | 37 | 0 | NR | NR |
| Kohler 2019 | 63 (med) | 20 | 21 | 1 | 20 | NR |
| Merritt 2020 | 61.6 | 99 | 130 | 0 | 112 | S:40<br>N:90 |
| Miro 2017 | 59.9 | 79 | 74 | 23 | NR | NR |
| Nguyen 2005 | 62 | 8 | NR | NR | NR | NR |
| Nguyen 2011 | 64.7 | 118 | 134 | 18 | 59 | NR |
| Perry 2009 | NR | NR | 32 | NR | NR | NR |
| Pham 2017 | 63.7 | 27 | 30 | 0 | 26 | S: 3<br>N: 27 |
| Prochazka 2018 | 61.2 | 30 | 33 | 0 | 17 | NR |
| Schroder 2010 | 56.8 | 349 | 419 | 0 | 210 | NR |

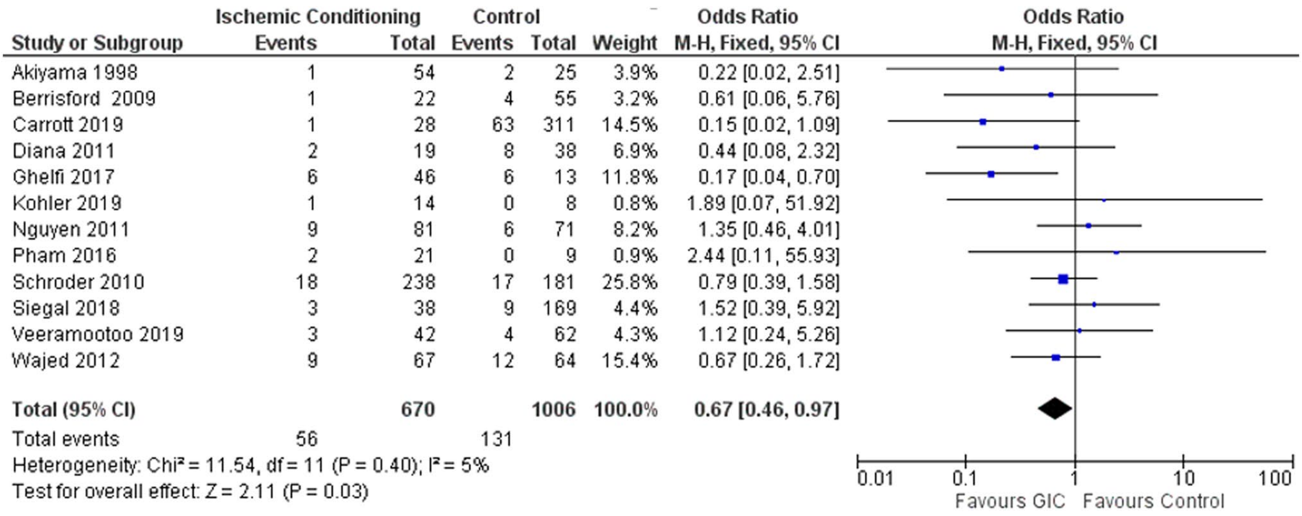
**Table 2** Characteristics of included studies

| Study | Type | Length of study, years | Comparator | Size, *n* | Control, *n* (%) | GIC, *n* | GIC method | GIC time to esophagectomy, days (mean) |
|---|---|---|---|---|---|---|---|---|
| Akiyama 1998 [5]<br>Japan | R | NR | GIC vs Control | 74 | 25 (34) | 54 | Angio | 14 |
| Berrisford 2009 [23]<br>UK | R | 3.2 | GIS vs Control | 77 | 55 (71) | 22 | Lap | 14 |
| Bludau 2012 [24]<br>Germany | P | 1.8 | None | 20 | 0 (0) | 20 | Lap | 4.5 |
| Carrott 2019 [25]<br>USA | R | NR | GIC vs Control | 339 | 311 (92) | 28 | Lap | Median 6 |
| Diana 2011 [26]<br>Switzerland | P | 9 | GIC vs Control | 57 | 38 (67) | 19 | Angio | 17 |
| Farran 2010 [7]<br>Spain | R | 6.9 | None | 39 | 0 (0) | 39 | Angio | 20.6 |
| Ghelfi 2017 [27]<br>USA | R | 6.8 | GIC vs Control | 59 | 13 (22) | 46 | Angio | 21 |
| Holscher 2007 [28]<br>Germany | R | 1.8 | None | 83 | 0 (0) | 83 | Lap | 4.3 |
| Isomura 1999 [29]<br>Japan | R | 2.9 | None | 37 | 0 (0) | 37 | Angio | 14 |
| Kohler 2019 [30]<br>Germany | R | NR | GIC vs Control | 22 | 8 (36) | 14 | Lap | 5 |
| Merritt 2020 [17]<br>USA | R | 4.1 | None | 130 | 0 (0) | 130 | Lap | 18.1 |
| Miro 2018 [18]<br>Spain | P | 13 | None | 96 | 1 (1) | 96 | Angio | 14 |
| Nguyen 2005 [13]<br>USA | P | NR | None | 9 | 0 (0) | 9 | Lap | 12 |
| Nguyen 2011 [14]<br>USA | R | NR | GIC vs Control | 152 | 71 (47) | 81 | Lap | 6 |
| Perry 2009 [31]<br>USA | R | 2.9 | GIC vs Control | 32 | 25 (78) | 7 | Lap | 1 week vs 2 weeks |
| Pham 2017 [32]<br>USA | P | 5.5 | None | 30 | 9 (30) | 21 | Lap | Partial: 163, Complete: 95 |
| Prochazka 2018 [33]<br>Czech Rep | R | 5.9 | None | 33 | 0 (0) | 33 | Lap | Median 29 vs median 49 |
| Schroder 2010 [34]<br>Germany | R | 11.9 | GIC vs Control | 419 | 181 (43) | 238 | Lap | 4.5 |
| Siegal 2018 [9]<br>USA | P | 5.9 | GIC vs Control | 207 | 169 (82) | 38 | Lap | 98 |
| Strosberg 2016 [19]<br>USA | P | 0.9 | None | 30 | 0 (0) | 30 | Lap | Median 14.5 |
| Veeramootoo 2010 [35]<br>UK | P | NR | GIC vs Control | 97 | 55 (57) | 42 | Lap | NR |
| Wajed 2012 [36]<br>UK | P |  | GIC vs Control | 131 | 64 (49) | 67 | Lap | 14 |
| Yetasook 2012 [37]<br>USA | R | 2.8 | None | 24 | 0 (0) | 24 | Lap | 6.7 |

*Angio* angiography, *Lap* laparoscopic, *NR* not recorded, *P* prospective cohort, *R* retrospective cohort

## No difference in odds of conduit ischemia between patients with GIC and patients without GIC

Conduit necrosis or ischemia was reported in 11 comparative studies, of which 8 reported laparoscopic GIC compared to three reporting angiographic GIC. No significant reduction in gastric conduit ischemia was noted in patients undergoing GIC (OR 0.40; 95% CI 0.13–1.23; $I^2 = 0\%$; $p = 0.11$) (Fig. 3).

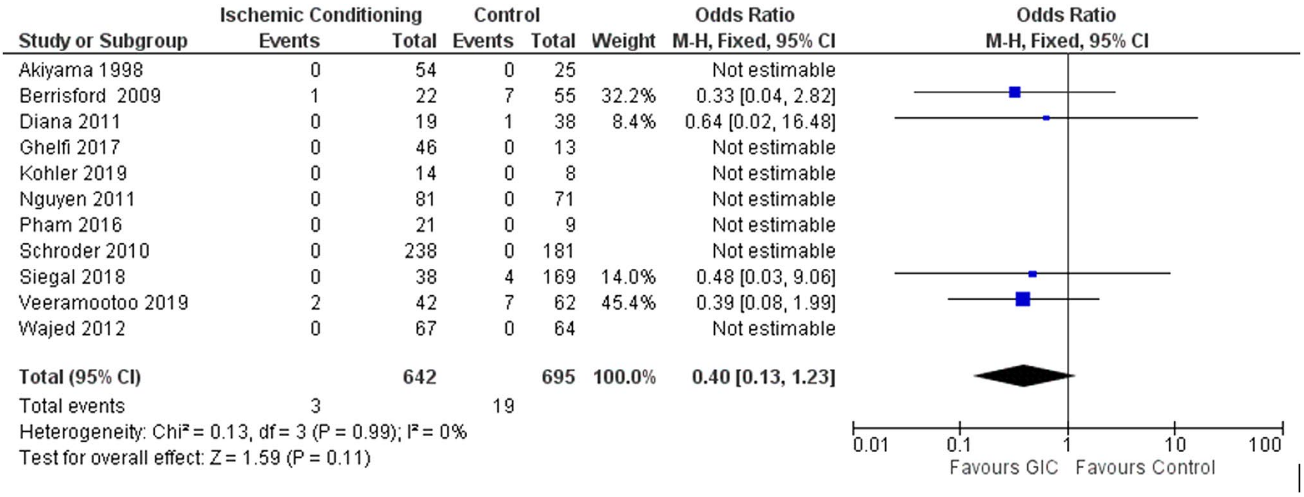


| Study or Subgroup | Ischemic Conditioning Events | Ischemic Conditioning Total | Control Events | Control Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Akiyama 1998 | 1 | 54 | 2 | 25 | 3.9% | 0.22 [0.02, 2.51] |
| Berrisford 2009 | 1 | 22 | 4 | 55 | 3.2% | 0.61 [0.06, 5.76] |
| Carrott 2019 | 1 | 28 | 63 | 311 | 14.5% | 0.15 [0.02, 1.09] |
| Diana 2011 | 2 | 19 | 8 | 38 | 6.9% | 0.44 [0.08, 2.32] |
| Ghelfi 2017 | 6 | 46 | 6 | 13 | 11.8% | 0.17 [0.04, 0.70] |
| Kohler 2019 | 1 | 14 | 0 | 8 | 0.8% | 1.89 [0.07, 51.92] |
| Nguyen 2011 | 9 | 81 | 6 | 71 | 8.2% | 1.35 [0.46, 4.01] |
| Pham 2016 | 2 | 21 | 0 | 9 | 0.9% | 2.44 [0.11, 55.93] |
| Schroder 2010 | 18 | 238 | 17 | 181 | 25.8% | 0.79 [0.39, 1.58] |
| Siegal 2018 | 3 | 38 | 9 | 169 | 4.4% | 1.52 [0.39, 5.92] |
| Veeramootoo 2019 | 3 | 42 | 4 | 62 | 4.3% | 1.12 [0.24, 5.26] |
| Wajed 2012 | 9 | 67 | 12 | 64 | 15.4% | 0.67 [0.26, 1.72] |
| **Total (95% CI)** | | **670** | | **1006** | **100.0%** | **0.67 [0.46, 0.97]** |
| Total events | 56 | | 131 | | | |

Heterogeneity: Chi² = 11.54, df = 11 (P = 0.40); I² = 5%

Test for overall effect: Z = 2.11 (P = 0.03)

**Fig. 2** Odds of post-operative anastomotic leaks among patients undergoing gastric ischemic conditioning versus controls. *GIC* gastric ischemic conditioning



| Study or Subgroup | Ischemic Conditioning Events | Ischemic Conditioning Total | Control Events | Control Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Akiyama 1998 | 0 | 54 | 0 | 25 | | Not estimable |
| Berrisford 2009 | 1 | 22 | 7 | 55 | 32.2% | 0.33 [0.04, 2.82] |
| Diana 2011 | 0 | 19 | 1 | 38 | 8.4% | 0.64 [0.02, 16.48] |
| Ghelfi 2017 | 0 | 46 | 0 | 13 | | Not estimable |
| Kohler 2019 | 0 | 14 | 0 | 8 | | Not estimable |
| Nguyen 2011 | 0 | 81 | 0 | 71 | | Not estimable |
| Pham 2016 | 0 | 21 | 0 | 9 | | Not estimable |
| Schroder 2010 | 0 | 238 | 0 | 181 | | Not estimable |
| Siegal 2018 | 0 | 38 | 4 | 169 | 14.0% | 0.48 [0.03, 9.06] |
| Veeramootoo 2019 | 2 | 42 | 7 | 62 | 45.4% | 0.39 [0.08, 1.99] |
| Wajed 2012 | 0 | 67 | 0 | 64 | | Not estimable |
| **Total (95% CI)** | | **642** | | **695** | **100.0%** | **0.40 [0.13, 1.23]** |
| Total events | 3 | | 19 | | | |

Heterogeneity: Chi² = 0.13, df = 3 (P = 0.99); I² = 0%

Test for overall effect: Z = 1.59 (P = 0.11)

**Fig. 3** Odds of conduit ischemia among patients undergoing gastric ischemic conditioning versus controls. *GIC* gastric ischemic conditioning

## Reduced odds of anastomotic strictures in patients with GIC

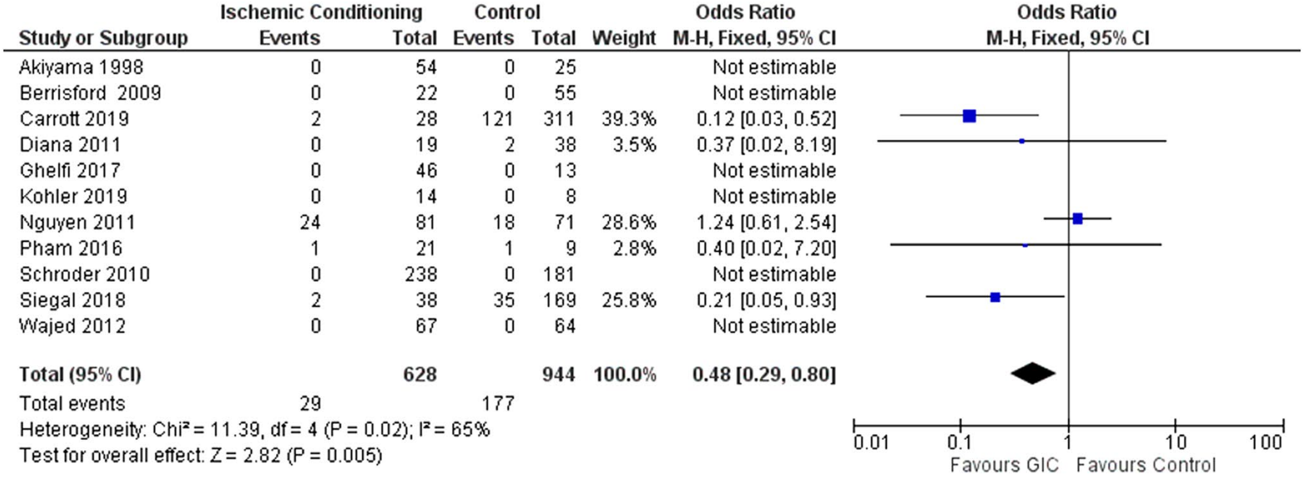
Anastomotic strictures were reported in 11 comparative studies, of which eight reported laparoscopic GIC compared to three reporting angiographic GIC. A significant reduction in anastomotic strictures was noted in patients undergoing GIC (OR 0.48; 95% CI 0.29–0.80; $I^2 = 65\%$; $p = 0.005$) (Fig. 4).

## No difference in odds of overall survival in patients with GIC and patients without GIC

Overall survival was reported in nine comparative studies, of which 6 reported laparoscopic GIC compared to three reporting angiographic GIC. No significant improvement in overall survival was noted (OR 0.54; 95% CI 0.29–1.02; $I^2 = 22\%$; $p = 0.06$) (Fig. 5).

## Description of outcomes using pooled proportions

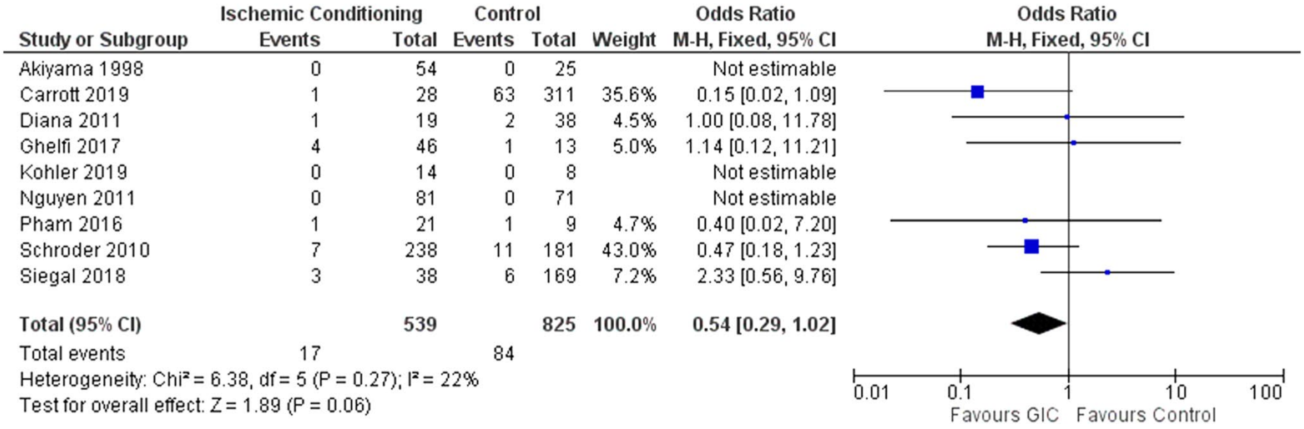
To gain insight into outcomes related to the technique, duration of IC, and number of vessels ligated, pooled data were examined (Supplementary Tables 4–6). Laparoscopic ischemic conditioning had a higher pooled proportion of stricture formations than angiographic (2% vs. 0%). Similar rates of ischemia (1.0% vs. 1.3%) and anastomotic leaks (7.8% vs. 6.8%) were noted among the two techniques. GIC for less than 7 days was associated with higher rates



| Study or Subgroup | Ischemic Conditioning Events | Ischemic Conditioning Total | Control Events | Control Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Akiyama 1998 | 0 | 54 | 0 | 25 | | Not estimable |
| Berrisford 2009 | 0 | 22 | 0 | 55 | | Not estimable |
| Carrott 2019 | 2 | 28 | 121 | 311 | 39.3% | 0.12 [0.03, 0.52] |
| Diana 2011 | 0 | 19 | 2 | 38 | 3.5% | 0.37 [0.02, 8.19] |
| Ghelfi 2017 | 0 | 46 | 0 | 13 | | Not estimable |
| Kohler 2019 | 0 | 14 | 0 | 8 | | Not estimable |
| Nguyen 2011 | 24 | 81 | 18 | 71 | 28.6% | 1.24 [0.61, 2.54] |
| Pham 2016 | 1 | 21 | 1 | 9 | 2.8% | 0.40 [0.02, 7.20] |
| Schroder 2010 | 0 | 238 | 0 | 181 | | Not estimable |
| Siegal 2018 | 2 | 38 | 35 | 169 | 25.8% | 0.21 [0.05, 0.93] |
| Wajed 2012 | 0 | 67 | 0 | 64 | | Not estimable |
| **Total (95% CI)** | | **628** | | **944** | **100.0%** | **0.48 [0.29, 0.80]** |
| Total events | 29 | | 177 | | | |

Heterogeneity: Chi² = 11.39, df = 4 (P = 0.02); I² = 65%
Test for overall effect: Z = 2.82 (P = 0.005)

**Fig. 4** Odds of anastomotic strictures among patients undergoing gastric ischemic conditioning versus controls. *GIC* gastric ischemic conditioning



| Study or Subgroup | Ischemic Conditioning Events | Ischemic Conditioning Total | Control Events | Control Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Akiyama 1998 | 0 | 54 | 0 | 25 | | Not estimable |
| Carrott 2019 | 1 | 28 | 63 | 311 | 35.6% | 0.15 [0.02, 1.09] |
| Diana 2011 | 1 | 19 | 2 | 38 | 4.5% | 1.00 [0.08, 11.78] |
| Ghelfi 2017 | 4 | 46 | 1 | 13 | 5.0% | 1.14 [0.12, 11.21] |
| Kohler 2019 | 0 | 14 | 0 | 8 | | Not estimable |
| Nguyen 2011 | 0 | 81 | 0 | 71 | | Not estimable |
| Pham 2016 | 1 | 21 | 1 | 9 | 4.7% | 0.40 [0.02, 7.20] |
| Schroder 2010 | 7 | 238 | 11 | 181 | 43.0% | 0.47 [0.18, 1.23] |
| Siegal 2018 | 3 | 38 | 6 | 169 | 7.2% | 2.33 [0.56, 9.76] |
| **Total (95% CI)** | | **539** | | **825** | **100.0%** | **0.54 [0.29, 1.02]** |
| Total events | 17 | | 84 | | | |

Heterogeneity: Chi² = 6.38, df = 5 (P = 0.27); I² = 22%
Test for overall effect: Z = 1.89 (P = 0.06)

**Fig. 5** Odds of overall survival among patients undergoing gastric ischemic conditioning versus controls. *GIC* gastric ischemic conditioning

of stricture formation (5.6% vs. 1.2%), while greater than 7 days was associated with higher rates of conduit ischemia (0.4% vs. 1.4%). The observed leak rate was similar among the two different time groups (7.6% vs. 7.3%). Anastomotic leak rates were higher in the single-vessel group (9.5% vs. 5.8%). Incidence of stricture formation was lower in the single-vessel group (1% vs. 4.3%), while conduit ischemia was similar (1.1% vs. 0.9%).

### Heterogeneity analysis and risk of bias

Heterogeneity was classified as low for anastomotic leaks ($I^2 = 5\%$), low for conduit ischemia ($I^2 = 0$), and low for overall survival ($I^2 = 22\%$). Heterogeneity was classified as moderate for anastomotic strictures ($I^2 = 65\%$).

## Comment

To our knowledge, this is the most recent systematic review and meta-analysis on GIC for patients undergoing esophagectomy. We found that GIC is associated with a significant decrease in anastomotic strictures and anastomotic leaks and was not associated with conduit ischemia. Importantly, we show that patients receiving GIC had 37% lower odds of anastomotic leaks and 52% lower odds of anastomotic stricture than those who did not undergo GIC.

The concept of GIC has drawn increasing interest, with two systematic reviews and meta-analyses published on this topic in recent years. Our findings are consistent with Zhou et al., who have reported a reduction in anastomotic leaks and stricture formation in their recent

2020 meta-analysis [15]. The authors conducted a subgroup analysis on their data, stratifying by method of GIC and noted that both laparoscopic and angiographic GIC reduced anastomotic leaks and stricture formation. Of note, the study did include data from abstract records reported in conference proceedings and did not explore ischemia of the gastric conduit as an outcome. Another review by Kamarajah et al. reported no significant difference in anastomotic leaks or anastomotic strictures in their meta-analysis [16]. Their search strategy resulted in a marked lower number of initial results and there have been further full-text articles published on this topic included in our analysis which may explain the contradictory results reported in our review [17–19]. Of note, the authors did not search the Web of Science or Scopus databases which we included in our systematic search and this may explain the decreased number of studies. Our review of the outcomes by pooled proportion reported in the literature for technique of GIC, timing of GIC, and number of vessels selected is an additional novel aspect of our review. While these findings are not statistically significant, the trends among the literature provide valuable and novel insight regarding the overall distribution of outcomes and may serve as an impetus and guide the development of prospective trials.

Our findings are supported by the theories of a microcellular or physiological change induced by ischemic conditioning in the gastric conduit. Urschel et al. hypothesized that ischemic conditioning may provide neovascularization of the remaining vessels, improving blood supply to the gastric conduit and thus reducing the risk of anastomotic breakdown or stricturing [5]. Contrary to this, a recently published randomized control trial by Veeramootoo et al. examined Doppler fluximetry of the gastric conduit comparing patients undergoing ischemic conditioning versus patients who did not and concluded no significant difference in perfusion among the groups [20]. They did not report on clinical outcomes in their study and thus were not included in the meta-analyses of this review. Although severity of the anastomotic leak was not an outcome of interest in this review, Heger et al. demonstrated that anastomotic leaks in ischemic conditioning were more likely to be managed conservatively [21]. While the exact theories through which GIC may impart clinical benefit are not clear, the promising findings of our work highlight the need for further studies which aim to elucidate its underlying mechanisms.

The utility of angiography to perform GIC was first discovered in Japan in the 1990s. Studies published by Akiyama et al. first demonstrated the efficacy of this procedure and reported positive results in terms of reduction of anastomotic leaks post-esophagectomy [5]. Laparoscopic ischemic conditioning was subsequently popularized and has been demonstrated as safe, with post-operative complications occurring rarely. We were unable to conduct meta-analysis comparing these two techniques, as none of the studies obtained provided direct comparison of these two techniques. However, comparison of outcomes by pooled proportion regarding these two techniques depicts higher proportion of leaks and strictures occurring in the laparoscopic group. One reason why this may have occurred is due to the physical manipulation of tissue, which occurs during laparoscopic surgery. This may induce microtrauma to the gastric tissue, increasing its vulnerability to ischemic insult and subsequent leaks and strictures. Despite the less invasive nature of angiographic GIC, however, from our included studies, this technique frequently embolizes the distal splenic artery, whereas this is not performed in laparoscopic GIC. This is associated with reports of pancreatitis and splenic infarction in the literature and thus may explain why angiographic GIC is less frequently performed, despite being the less invasive modality [6, 7]. Laparoscopically, the most commonly selected arteries included the left gastric and short gastric arteries, with some studies including the right gastric artery, as well. In angiographic GIC, it is more common for all three arteries to be selected. The most preferred gastric vessels remain unclear, but the majority of studies have emphasized the selection of the left gastric and short gastric arteries. From the literature to date, it appears that the preferred mechanism of ischemic conditioning has yet to be elucidated, and further research should be directed within this area.

We observed that single-vessel GIC was associated with higher incidence of anastomotic strictures, but lower incidence of stricture formation, compared to multi-vessel GIC. The causal mechanism for why this may occur is unclear. However, presuming the notion that GIC does indeed promote neovascularization, it follows that multi-vessel GIC may elicit a more potent stimuli for neovascularization. This process ultimately increases the blood flow to the anastomosis, promotes healing, and reduces the risk of breakdown and leaks. This may explain the first finding of why single-vessel GIC was associated with higher rates of anastomotic leaks. The rational for why single-vessel GIC was associated with less stricture formation is more nuanced. It has been reported in the literature that stricture formation can be a consequence of relative ischemia to the anastomosis [22]. Perhaps the increased ischemia prior to neovascularization in the multi-vessel GIC group increases the risk of stricture formation. Ischemic conditioning for less than 7 days was associated with higher rates of leaks and strictures. This supports the theory that a greater interval period allows for higher amounts of neovascularization. These observations should be taken with the caveat that the data are obtained from non-standardized studies without direct comparator groups to truly investigate these findings and are subject to confounding variables.

There are a number of limitations to this review. The included studies contain very limited baseline characteristics regarding their study population, not providing smoking status, major cardiopulmonary co-morbidities, and ASA or CCI co-morbidity scores. No randomized control trials meeting the inclusion and exclusion criteria of our search were identified and our findings are largely based on retrospective data. The included studies encompass a broad timeline, from 1996 to 2020, and much has changed in the interim regarding treatment of esophageal cancer. With the publication of the CROSS trial in 2015, neoadjuvant therapy has become standard of care, and it is unclear how the administration of radiation and chemotherapeutic agents impacts ischemic conditioning [23]. Of note, 15 of the 23 studies did report neoadjuvant therapy in patients undergoing GIC, with 9 studies published after the CROSS trial. Furthermore, centers may be reluctant to endorse ischemic conditioning in the post-neoadjuvant, but pre-operative period, given the priority of ensuring an expedited recovery to proceed to esophagectomy in a timely fashion. Introducing an additional procedure in this interim period may ultimately delay esophagectomy or induce a complication precluding curative therapy. Thus, identification of patients who are at high risk for anastomotic complications may allow for the determination of a sub-group who may benefit most from GIC, understanding that this is a calculated risk weighing the benefit of GIC against its potential complications. Regarding our statistical analysis, we used a fixed-effects model, and heterogeneity was demonstrated to be low for anastomotic leaks, conduit ischemia, and overall survival through determination of the $I^2$ statistic. However, there was moderate heterogeneity demonstrated in the meta-analysis of conduit strictures, and thus a random-effects model may have been more appropriate for evaluation of this outcome. We elected to pursue a fixed-effects model to preserve uniformity in the interpretation of our meta-analysis. Given that esophagectomy is most commonly performed for oncologic indications, an additional major limitation of the research is the near complete absence of oncology data among the included studies. Lastly, there still remains many unanswered questions regarding the optimal timing, technique, and number of vessels to ligate during GIC.

Despite the limitations of the current literature, the findings of decreased anastomotic leak and stricture rates obtained in this review have notable implications, particularly in a patient population that is high risk for post-operative complications. Ischemic conditioning of the gastric conduit may reduce rates of anastomotic leaks and stricture formation in patients undergoing esophagectomy. However, the sparsity of prospective data particularly in the form of a randomized control trials evaluating patient outcomes limits the reliability of this data. Furthermore, the potential benefit offered by ischemic conditioning must be balanced against the increased recovery time, operative concerns regarding adhesion genesis, tolerance of chemotherapeutic agents, and cost to both the patient and healthcare system, factors that were not accounted for in the reviewed studies. However, for patients with major risk factors for anastomotic leak, such as heart failure, hypertension, radiation, or renal insufficiency, ischemic conditioning may serve as an important therapeutic tool [3]. Future research on ischemic conditioning should thus be directed at determining the optimal timing, number of vessels ligated, and technique employed, as these remain unanswered questions.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00464-021-08866-4.

**Acknowledgements** The research team would like to thank the University of Alberta's library service for facilitating inter-library loans for inaccessible research articles during this review.

**Funding** No funding was secured for this systematic review and meta-analysis.

## Declarations

**Disclosures** Drs. Jogiat, Sun, Dang, Mocanu, Karmali, Turner, and Switzer have no conflict of interest or financial ties to disclose. Librarian Janice Kung has no conflict of interest or financial ties to disclose.

**Ethical approval** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## References

1. Markar S, Gronnier C, Duhamel A, Mabrut Y, Bail J, Carrere N, Lefevre J, Brigand C, Vaillant J, Adham M, Msika S, Demartines N, Nakada I, Meunier B, Collet D, Mariette C (2015) The impact of severe anastomotic leak on long-term survival and cancer recurrence after surgical resection for esophageal malignancy. Ann Surg 262:972–980
2. McCulloch P, Ward J, Tekkis P (2003) Mortality and morbidity in gastro-oesophageal cancer surgery: initial results of ASCOT multicentre prospective cohort study. BMJ 327:1192–1196
3. Kassis E, Kosinski A, Ross P, Koppes K, Donahue J, Daniel V (2013) Predictors of anastomotic leak after esophagectomy: an analysis of the society of thoracic surgeons general thoracic database. Ann Thorac Surg 30:1919–1926
4. Markar SR, Arya S, Karthikesalingam A, Hanna GB (2013) Technical factors that affect anastomotic integrity following esophagectomy: systematic review and meta-analysis. Ann Surg 20:4274–4281
5. Urschel J (1995) Ischemic conditioning of the rat stomach: Implications for esophageal replacement with stomach. J Cardiovasc Surg 36:191–193
6. 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 120:542–546

7. Farran L, Miro M, Alba E, Bettonica C, Aranda H, Galan M, Rafecas A (2011) Preoperative gastric conditioning in cervical gastroplasty. Dis Esophagus 24:205–210
8. Prochazka V, Marek F, Kunovsky L, Svaton R, Grolich T, Moravcik P, Farkasova M, Kala Z (2018) Comparison of cervical anastomotic leak and stenosis after oesophagectomy for carcinoma according to the interval of the stomach ischaemic conditioning. Ann R Coll Surg Engl 100:509–514
9. Siegal S, Parmar A, Haisley K, Tieu B, Schipper P, Hunter J, Dolan J (2018) Gastric ischemic conditioning prior to esophagectomy is associated with decreased stricture rate and overall anastomotic complications. J Gastrointest Surg 22:1501–1507
10. Prudius V, Prochazka V, Pavlovsky Z, Pestal A, Vlcek P, Capov I, Veverkova L, Reska M (2018) Neovascularization after ischemic conditioning of the stomach and the influence of follow-up neoadjuvant chemotherapy thereon. Wideochir Inne Tech Maloinwazyjne 13:299–305
11. Higgins J, Thompson S, Deeks J, Altman D (2003) Measuring inconsistency in meta-analyses. BMJ 327:557–560
12. Hozo S, Djulbegovic B, Hozo I (2005) Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 5:13
13. Nguyen N, Longoria M, Sabio A, Chalifoux S, Lee J, Chang K, Wilson S (2006) Preoperative laparoscopic ligation of the left gastric vessels in preparation for esophagectomy. Ann Thorac Surg 81:2318–2320
14. Nguyen N, Nguyen X, Reavis K, Elliot C, Masoomi H, Stamos M (2012) Minimally invasive esophagectomy with and without gastric ischemic conditioning. Surg Endosc 26:1637–1641
15. Zhou Z, Shen X, Song T, Xu Z, Alai G, Yao P, Lin Y (2020) The efficacy of ischemic conditioning in the prevention of gastroesophageal anastomotic complications: a meta-analysis. Ann Palliat Med 9:569
16. Kamarajah S, Boyle C, Bundred J, Tan B (2020) Critical appraisal of gastric conduit ischaemic conditioning (GIC) prior to oesophagectomy: a systematic review and meta-analysis. Int J Surg 77:77–82
17. Merritt R, Kneuertz P, D'Souza D, Perry K (2020) A successful clinical pathway protocol for minimally invasive esophagectomy. Surg Endosc 34:1696–1703
18. Miró M, Farran L, Estremiana F, Miquel J, Escalante E, Aranda H, Bettonica C, Galan M (2018) Does gastric conditioning decrease the incidence of cervical oesophagogastric anastomotic leakage? Cirugia Española 96:102–108
19. Strosberg D, Merritt R, Perry K (2017) Preventing anastomotic complications: early results of laparoscopic gastric devascularization two weeks prior to minimally invasive esophagectomy. Surg Endosc 31:1371–1375
20. Veeramootoo D, Shore A, Wajed S (2012) Randomized controlled trial of laparoscopic gastric ischemic conditioning prior to minimally invasive esophagectomy, the LOGIC trial. Surg Endosc 26:1822–1829
21. Heger P, Blank S, Diener M, Ulrich A, Schmidt T, Buchler M, Mihaljevic A (2017) Gastric preconditioning in advance of esophageal resection-systematic review and meta-analysis. J Gastrointest Surg 21:1523–1532
22. Chung R, Hitch D, Armstrong D (1988) The role of tissue ischemia in the pathogenesis of anastomotis stricture. Surgery 104:824–829
23. Shapiro J, van Lanschot J, Hulshof M, van Hagen P, Henegouwen M, Wijnhoven B, van Laarhoven H, Nieuwenhuijzen G, Hospers G, Bonenkamp J, Cuesta M, Blaisse R, Busch O, Ten Kate F, Creemers G, Punt C, Plukker J, Verheul H, Bilgen E, van Dekken H, van der Sangen M, Rozema T, Biermann K, Beukema J, Piet A, van Rij C, Reinders J, Tilanus H, Steyerberg E, Gaast A (2015) Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 16:1090–1098
24. 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 36:888–893
25. Bludau M, Hölscher AH, Vallböhmer D, Metzger R, Bollschweiler E, Schröder W (2013) Vascular endothelial growth factor expression following ischemic conditioning of the gastric conduit. Dis Esophagus 26:847–852
26. Carrott P, Miller J, Chang A, Reddy R, Lin J, Lagisetty K (2019) Gastric ischemic conditioning before esophagectomy: timing and method matter. J Am Coll Surg 229:207–208
27. Diana M, Hübner M, Vuilleumier H, Bize P, Denys A, Demartines N, Shafer M (2011) Redistribution of gastric blood flow by embolization of gastric arteries before esophagectomy. Ann Thorac Surg 91:1546–1551
28. Ghelfi J, Brichon P, 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 40:712–720
29. Holscher Ah, Pm S, Gutschow C, Schröder W (2007) Laparoscopic ischemic conditioning of the stomach for esophageal replacement. Ann Surg 245:241–246
30. Isomura T, Itoh S, Endo T, Akiyama S, Maruyama K, Ishiguchi T, Ishigaki T, Takagi H (1999) Efficacy of gastric blood supply redistribution by transarterial embolization: Preoperative procedure to prevent postoperative anastomotic leaks following esophagoplasty for esophageal carcinoma. Cardiovasc Intervent Radiol 22:119–123
31. Köhler H, Jansen-Winkeln B, Maktabi M, Barberio M, Takoh J, Holfert N, Moulla Y, Niebisch S, Diana M, Neumuth T, Rabe S, 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 33:3775–3782
32. Perry K, Enestvedt K, Pham T, Hunter J (2009) Laparoscopic ischemic pre-conditioning of gastric conduit: reducing anastomotic complications of minimally invasive esophagectomy. Gastroenterology 136:5
33. Pham T, Melton S, McLaren P, Mokdad A, Huerta S, Wang D, Perry K, Hardaker H, Dolan J (2017) Laparoscopic ischemic conditioning of the stomach increases neovascularization of the gastric conduit in patients undergoing esophagectomy for cancer. J Surg Oncol 116:391–397
34. Prochazka V, Marek F, Kunovsky L, Svaton R, Grolich T, Moravcik P, Farkasova M, Zala K (2018) Comparison of cervical anastomotic leak and stenosis after oesophagectomy for carcinoma according to the interval of the stomach ischaemic conditioning. Ann R Coll Surg Engl 100:509–514
35. Schröder W, Hölscher A, Bludau M, Vallböhmer D, Bollschweiler E, Gutschow C (2010) Ivor-lewis esophagectomy with and without laparoscopic conditioning of the gastric conduit. World J Surg 34:738–743
36. Veeramootoo D, Shore A, Shields B, Krishnadas R, Cooper M, Berrisford R, Wajed S (2010) Ischemic conditioning shows a time-dependant influence on the fate of the gastric conduit after minimally invasive esophagectomy. Surg Endosc 24:1126–1131
37. Wajed S, Veeramootoo D, Shore A (2012) Surgical optimisation of the gastric conduit for minimally invasive oesophagectomy. Surg Endosc 26:271–276