Critical appraisal of gastric conduit ischaemic conditioning (GIC) prior to oesophagectomy

Kamarajah, Sivesh K.; Boyle, Charlie; Bundred, James R.; Tan, Benjamin H. L.

DOI:
10.1016/j.ijsu.2020.03.020

Document Version
Peer reviewed version

Citation for published version (Harvard):
Kamarajah, SK, Boyle, C, Bundred, JR & Tan, BHL 2020, 'Critical appraisal of gastric conduit ischaemic conditioning (GIC) prior to oesophagectomy: a systematic review and meta-analysis', *International journal of surgery (London, England)*, vol. 77, pp. 77-82. https://doi.org/10.1016/j.ijsu.2020.03.020

Journal Pre-proof

Critical Appraisal of Gastric Conduit Ischaemic Conditioning (GIC) prior to Oesophagectomy: A Systematic Review and Meta-Analysis

Sivesh K. Kamarajah, Charlie Boyle, James R. Bundred, Benjamin HL. Tan

PII: S1743-9191(20)30232-6

DOI: https://doi.org/10.1016/j.ijsu.2020.03.020

Reference: IJSU 5326

To appear in: *International Journal of Surgery*

Received Date: 16 December 2019

Revised Date: 12 March 2020

Accepted Date: 13 March 2020

Please cite this article as: Kamarajah SK, Boyle C, Bundred JR, Tan BH, Critical Appraisal of Gastric Conduit Ischaemic Conditioning (GIC) prior to Oesophagectomy: A Systematic Review and Meta-Analysis, *International Journal of Surgery*, https://doi.org/10.1016/j.ijsu.2020.03.020.

Critical Appraisal of Gastric Conduit Ischaemic Conditioning (GIC) prior to Oesophagectomy: A Systematic Review and Meta-Analysis

Sivesh K Kamarajah[1, 2], Charlie Boyle[1], James R Bundred,[3] Benjamin HL Tan[4]

1. Department of HPB and Transplant Surgery, The Freeman Hospital, Newcastle upon Tyne, Tyne and Wear, United Kingdom
2. Institute of Cellular Medicine, University of Newcastle, Newcastle upon Tyne, Tyne and Wear, United Kingdom
3. College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom
4. Department of Upper Gastrointestinal Surgery, Queen Elizabeth Hospital Birmingham, United Kingdom

Running Title: Gastric Conditioning for Oesophagectomy

Corresponding Author:

Mr Benjamin HL Tan MD, FRCS

Department of Upper Gastrointestinal Surgery

Queen Elizabeth Hospital Birmingham

United Kingdom

Email: benjamin.tan@uhb.nhs.uk

Manuscript Type: Original Article

Number of Text Pages: 11

Number of Tables: 3

Number of Figures: 1

Word Count: 1927

Funding source: None declared

Conflict of interest: None declared

Critical Appraisal of Gastric Conduit Ischaemic Conditioning (GIC) prior to Oesophagectomy: A Systematic Review and Meta-Analysis

Abstract

Introduction

Anastomotic leaks remain a major complication following oesophagectomy, accounting for high morbidity and mortality. Recently, gastric ischaemic conditioning (GIC) has been proposed to improve anastomotic integrity through neovascularisation of the gastric conduit. This systematic review and meta-analysis aim to determine the impact of GIC on postoperative outcomes following oesophagectomy.

Methods

A systematic literature search was performed to identify studies reporting GIC for any indication of oesophageal resection up to 25th April 2019. The primary outcome was anastomotic leak. Secondary outcomes were conduit necrosis, anastomotic strictures, overall and major complications or in-hospital mortality. Meta-analyses were conducted using random-effects modelling.

Results

Nineteen studies reported on GIC, of which 13 were comparative studies. GIC was performed through ligation in 13 studies and embolisation in six studies. GIC did not appear to reduce anastomotic leakages (OR 0.80, $CI_{95:}$ 0.51 - 1.24, p=0.3), anastomotic strictures (OR 0.75, $CI_{95:}$ 0.35 - 1.60, p=0.5), overall complications (OR 1.02, $CI_{95:}$ 0.48 - 2.16, p=0.9), major complications (OR 1.06, $CI_{95:}$ 0.53 - 2.11, p=0.9), or in-hospital mortality (OR 0.70, $CI_{95:}$ 0.32 - 1.53, p=0.4). However, GIC was

associated with reduced rates of conduit necrosis (OR 0.30, $CI_{95:}$ 0.11 - 0.77, p=0.013).

Conclusion

GIC does not appear to reduce overall rates of anastomotic leakage after oesophagectomy but seems to reduce severity of leakages. More in depth studies are recommended.

Introduction

Oesophageal cancers remain the sixth most common cause of cancer-related deaths worldwide.(1) Whilst multimodality treatment has improved long-term survival of patients with oesophageal cancers, oesophagectomy remains the mainstay of curative treatment.(2) Anastomotic leaks remain a major complication following oesophagectomy (3) with mortality rates ranging between 5% - 9%.(4-8) They are also associated with longer hospital stays, increased hospital costs,(3, 9) and have been demonstrated to adversely impact both overall (median: 36 vs 55 months) and disease-free survival (median: 34 vs 48 months).(3) While there is growing literature on the burden of anastomotic leaks, the factors associated with anastomotic leaks are poorly understood.(10, 11) Several factors have been thought to impact on anastomotic leaks such as location of the anastomosis and reconstruction technique of performing the oesophagogastric anastomosis.(12)

Over the last few years, there has been increasing interest in the role of gastric ischaemic conditioning (GIC) prior to oesophagectomy. Early evidence from animal experiments appear to demonstrate that partial devascularisation of the proximal stomach prior to oesophagectomies improves the perfusion of the proximal stomach. This therefore enhances the oesophagogastric anastomosis following surgery.(13) Several randomised controlled trials (RCTs) have evaluated the impact of ischaemic conditioning of the gastric tube, either by embolisation of the left gastric artery(14) or by laparoscopic ligation of the left gastric artery and/or short gastric arteries(15) prior to oesophagectomy. Although some of the RCTs performed an early oesophagectomy after GIC within a few days,(14, 16) others performed an

oesophagectomy more than 2 weeks after GIC.(17, 18) As a result, there remains no consensus on the timing of surgery following GIC to date.

Given uncertainty on the current evidence on the benefits of GIC prior to oesophagectomy, this systematic review aims to summarise the evidence on the methods of GIC, the time period from GIC to oesophagectomy, and assess the impact of GIC on postoperative morbidity (i.e. anastomotic leaks and conduit necrosis) and mortality.

Methods

Search Strategy

A systematic search of PubMed, EMBASE and the Cochrane Library databases were conducted on the 25th April 2019 by two independent investigators (SKK, CB). The search terms used were 'gastric ischaemic conditioning' or 'laparoscopic conditioning' and 'oesophagectomy' or 'esophagectomy' individually or in combination and they are presented as shown in Supplementary Table 1. A manual search of reference lists in recent reviews or from eligible studies were also performed to ensure that no pertinent studies were missed.(19) This paper was reported according to the with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (20, 21) and Assessing the methodological quality of systematic reviews (AMSTAR)(22) guidelines and prospectively registered on the PROSPERO database (Registration CRD42019137432) as previously reported.(19)

Inclusion and Exclusion Criteria

Inclusion criteria for this review were: (1) studies reporting GIC (through any method) in human subjects undergoing oesophagectomy for any indication; (2) studies published in English language. Exclusion criteria were: (1) Conference abstracts, review articles, and case reports (<5 patients). Following exclusion of duplicates, two researchers (SKK, CB) independently evaluated titles and abstracts of studies identified from the literature search. In the event where a study was considered to be potentially relevant to the research question, a full copy of the publication was obtained for a full text review.(21) Any areas of disagreement in study inclusion or exclusion between the two primary researchers (SKK, CB) were resolved through discussion and discussion with the senior author (BT).

Study Outcomes

The primary outcome measure was anastomotic leaks. The secondary outcome measures were anastomotic strictures, conduit necrosis, overall complications (Grade I-V) and major complications (≥Grade III) reported according to Clavien-Dindo Classification,(23) pulmonary complications and in-hospital mortality.

Data Extraction

Two primary researchers (SKK, CB) independently extracted data on study characteristics (author, year of publication, country of origin, study design (retrospective/prospective cohort study, RCTs), patient number with and without GIC), patient demographics (age, sex), method and details of GIC and reported clinical outcomes of interest as described above.

Assessment of methodological quality

Methodological quality and standard of outcome reporting within included studies were assessed by two independent researchers (SKK, JB). Methodological quality was formally assessed using the Newcastle-Ottawa score for cohort studies (SKK, JB).

Statistical analysis

This systematic review and meta-analysis was conducted in accordance with the recommendations of the Cochrane Library and PRISMA guidelines as described above.(24) Statistical significance was considered when $p<0.05$ and all analyses were performed using the R Foundation Statistical software (R 3.2.1) and Stata 15 (Version 15.1, StataCorp, College Station, Texas) as previously reported.(21, 25)

Analysis was performed by calculating the odds ratio (OR) for categorical variables. The random effects (DerSimonian-Laird) method was used for the meta-analysis of all outcomes. The I_2 value was to assess the degree of heterogeneity between studies and I_2 values were considered to represent low, moderate, and high degrees of heterogeneity where values were <25%, 25–75%, and >75%, respectively. Assessment of small study bias was carried out through visual assessment of funnel plots and egger regressions as previously reported.(21, 26, 27)

Results

Study Characteristics

This literature review identified 19 studies as reported according to the PRISMA guidelines (21, 26) (Figure 1). Baseline characteristics of included studies are presented in Table 1 and 2. This study included 1,596 patients undergoing oesophagectomy, of which 56% (n=890) received gastric ischaemic conditioning. Of the included 19 studies, 13 studies reported ligation technique and five studies reported embolisation techniques. A summary of quality assessment of included studies are presented in Supplementary Table 2.

Anastomotic Leaks

Anastomotic leaks were reported in 11 studies, of which seven reported ligation and three reported utilising the embolization technique for GIC. There were no significant differences in anastomotic leaks in patients with and without GIC (OR: 0.80, p=0.3) (Table 3). However, in patients undergoing embolisation, rates of anastomotic leaks were significantly lower in those undergoing GIC (OR: 0.25, p=0.005).

Conduit Necrosis

Conduit necrosis was reported in four studies, all of which used the ligation technique for GIC. There were significantly lower rates of conduit necrosis in patients undergoing GIC (OR: 0.30, p=0.013).

Anastomotic Strictures

Anastomotic strictures were reported in five studies of which three reported ligation and two reported the embolization technique. There was no significant difference in

stricture rates in the entire cohort (OR: 0.75, p=0.5) in patients with and without ischaemic preconditioning (Table 3).

Overall and Major Complications

Overall and major complications were reported in five and three studies respectively. There was no significant differences in rates of overall (OR: 1.02, p=0.9) and major (OR: 1.06, p=0.9) complications in the entire cohort in patients with and without ischaemic preconditioning (Table 3)

Pulmonary Complications

Pulmonary complications were reported in five studies, of which one did not report the technique used. There was no significant difference in rates of pulmonary complications (OR: 0.90, p=0.6) in patients with and without ischaemic preconditioning (Table 3)

In-hospital Mortality

In-hospital mortality was reported in seven studies, of which four reported ligation and two reported the embolisation technique. One study did not report the technique used. There was no significant difference in rates of in-hospital mortality (OR: 0.70, p=0.4) in patients with and without ischaemic preconditioning (Table 3)

Discussion

Oesophagectomy is recognised as one of the most morbidity-prone surgical procedures, associated with anastomotic leak rates as high as 40%.(3, 12) Although mortality rates following oesophagectomy have reduced significantly to below 5% in tertiary specialist centres over the last decade from 30% in the 1970s,(12) with studies demonstrating improvement in mortality rates in high-volume units compared to low-volume units,(28, 29) the morbidity rates following oesophagectomy remain high and range between 30% - 50%.(30, 31) Anastomotic leaks remain a major complication occurring in up to 40% of cases, requiring immediate treatment.(32) Whilst cervical anastomoses are recognised to be associated with higher risk of developing anastomotic leaks;(33, 34) thoracic anastomotic leaks are more likely to develop serious complications and consequently require surgical re-exploration.(30, 33) To improve anastomotic leak rates following oesophagectomy, preoperative ischaemic conditioning of the stomach conduit has been proposed by several groups as a new strategy to tackle this.

This systematic review and meta-analysis demonstrate that GIC prior to oesophagectomy is feasible and safe either by surgical ligation or by embolisation. In addition, this study has highlighted that GIC by embolization and not ligation was associated with significantly lower rates of anastomotic leaks and conduit necrosis. However, this systematic review did not demonstrate any differences for other endpoints studied such as anastomotic stricture rate, overall and major complications, pulmonary complications and in-hospital mortality.

This study also highlights that GIC is a safe procedure. It is associated with lower anastomotic complications after oesophagectomy, with comparable overall morbidity and mortality profile. This may be explained by several factors. Firstly, selective ligation of the gastric blood supply may result in neovascularisation of the remaining vessels, hence improving blood flow to the site of conduit anastomosis and an associated increase in tissue oxygenation.(35-39) These findings highlight a protective impact on the anastomosis during critical initial healing, leading to reduced risk of anastomotic complications. Secondly, during the oesophagectomy, the stomach does not need to be manipulated to the same extent that a non-GIC stomach does, which is less traumatic to the future conduit.

There are several limitations to this study. Firstly, included studies exhibit a high risk of bias, as these were single-centre, retrospective studies,(15, 17, 40) and reported unclear outcome definitions, specifically for anastomotic leaks or follow-up. Secondly, no randomised controlled trials (RCTs) that adequately adjusts for all confounding factors exist. However, this is largely a reflection on the lack of adoption of GIC in wider centres to allow a high-powered RCT to be conducted. Thirdly, variation in the GIC protocols exist due to the different waiting times and techniques (i.e. ligation or embolisation of the left gastric artery). Only one study(41) evaluated the efficacy of additional ligation of other arterial branches (i.e., short gastric vessels) which enhanced the effect of ischaemic preconditioning, but total patient numbers are too small to draw a meaningful conclusion. As a result, further evaluation of this aspect is required. As current guidelines recommend neoadjuvant therapy regimes in locally advanced oesophageal cancer,(42-44) the benefits of GIC in these settings cannot be answered. This is because if GIC were to be carried out during staging

laparoscopy prior to neoadjuvant treatment, the waiting time between GIC and oesophageal resection may be longer (>5 weeks) than in all of the current studies identified in this systematic review.

Conclusion

This systematic review and meta-analysis demonstrate that GIC before oesophagectomy appears to be feasible and safe but does not significantly reduce the rate of postoperative anastomotic leakage or stricture, major complications, or in-hospital mortality. Based on these results, preconditioning cannot generally be recommended for patients undergoing oesophagectomy. However, evaluation of GIC in the context of high-quality RCTs should explore various technical modifications (e.g. ligation of additional vessels to the left gastric artery), unstudied clinical settings (neoadjuvant therapy), and in high-risk groups (patients with visceral atherosclerosis).

Provenance and peer review

Not Commissioned, internally reviewed

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.

2. Van Daele E, Van de Putte D, Ceelen W, Van Nieuwenhove Y, Pattyn P. Risk factors and consequences of anastomotic leakage after Ivor Lewis oesophagectomydagger. Interact Cardiovasc Thorac Surg. 2016;22(1):32-37.

3. Markar S, Gronnier C, Duhamel A, Mabrut JY, Bail JP, Carrere N, et al. The Impact of Severe Anastomotic Leak on Long-term Survival and Cancer Recurrence After Surgical Resection for Esophageal Malignancy. Ann Surg. 2015;262(6):972-980.

4. Rutegard M, Lagergren P, Rouvelas I, Lagergren J. Intrathoracic anastomotic leakage and mortality after esophageal cancer resection: a population-based study. Ann Surg Oncol. 2012;19(1):99-103.

5. Junemann-Ramirez M, Awan MY, Khan ZM, Rahamim JS. Anastomotic leakage post-esophagogastrectomy for esophageal carcinoma: retrospective analysis of predictive factors, management and influence on longterm survival in a high volume centre. Eur J Cardiothorac Surg. 2005;27(1):3-7.

6. Sauvanet A, Mariette C, Thomas P, Lozac'h P, Segol P, Tiret E, et al. Mortality and morbidity after resection for adenocarcinoma of the gastroesophageal junction: predictive factors. J Am Coll Surg. 2005;201(2):253-262.

7. Griffin SM, Shaw IH, Dresner SM. Early complications after Ivor Lewis subtotal esophagectomy with two-field lymphadenectomy: risk factors and management. J Am Coll Surg. 2002;194(3):285-297.

8. Jamieson GG, Mathew G, Ludemann R, Wayman J, Myers JC, Devitt PG. Postoperative mortality following oesophagectomy and problems in reporting its rate. Br J Surg. 2004;91(8):943-947.

9. Goense L, van Dijk WA, Govaert JA, van Rossum PS, Ruurda JP, van Hillegersberg R. Hospital costs of complications after esophagectomy for cancer. Eur J Surg Oncol. 2017;43(4):696-702.

10. Low DE, Alderson D, Cecconello I, Chang AC, Darling GE, D'Journo XB, et al. International Consensus on Standardization of Data Collection for Complications Associated With Esophagectomy: Esophagectomy Complications Consensus Group (ECCG). Ann Surg. 2015;262(2):286-294.

11. Low DE, Kuppusamy MK, Alderson D, Cecconello I, Chang AC, Darling G, et al. Benchmarking Complications Associated with Esophagectomy. Ann Surg. 2019;269(2):291-298.

12. Markar SR, Arya S, Karthikesalingam A, Hanna GB. Technical factors that affect anastomotic integrity following esophagectomy: systematic review and meta-analysis. Ann Surg Oncol. 2013;20(13):4274-4281.

13. Urschel JD. Ischemic conditioning of the rat stomach: implications for esophageal replacement with stomach. J Cardiovasc Surg (Torino). 1995;36(2):191-193.

14. Akiyama S, Ito S, Sekiguchi H, Fujiwara M, Sakamoto J, Kondo K, et al. Preoperative embolization of gastric arteries for esophageal cancer. Surgery. 1996;120(3):542-546.

15. Berrisford RG, Veeramootoo D, Parameswaran R, Krishnadas R, Wajed SA. Laparoscopic ischaemic conditioning of the stomach may reduce gastric-conduit

morbidity following total minimally invasive oesophagectomy. Eur J Cardiothorac Surg. 2009;36(5):888-893.

16. Schroder W, Holscher AH, Bludau M, Vallbohmer D, Bollschweiler E, Gutschow C. Ivor-Lewis esophagectomy with and without laparoscopic conditioning of the gastric conduit. World J Surg. 2010;34(4):738-743.

17. Veeramootoo D, Shore AC, Shields B, Krishnadas R, Cooper M, Berrisford RG, et al. Ischemic conditioning shows a time-dependant influence on the fate of the gastric conduit after minimally invasive esophagectomy. Surg Endosc. 2010;24(5):1126-1131.

18. Diana M, Hubner M, Vuilleumier H, Bize P, Denys A, Demartines N, et al. Redistribution of gastric blood flow by embolization of gastric arteries before esophagectomy. Ann Thorac Surg. 2011;91(5):1546-1551.

19. Bundred J, Kamarajah SK, Roberts KJ. Body composition assessment and sarcopenia in patients with pancreatic cancer: a systematic review and meta-analysis. HPB (Oxford). 2019;21(12):1603-1612.

20. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.

21. Kamarajah SK, Bundred J, Tan BHL. Body composition assessment and sarcopenia in patients with gastric cancer: a systematic review and meta-analysis. Gastric Cancer. 2019;22(1):10-22.

22. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10.

23. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250(2):187-196.

24. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008-2012.

25. Kamarajah SK, Sutandi N, Robinson SR, French JJ, White SA. Robotic versus conventional laparoscopic distal pancreatic resection: a systematic review and meta-analysis. HPB (Oxford). 2019; 21(9):1107-1118

26. Bundred J, Kamarajah SK, Roberts KJ. Body composition assessment and sarcopenia in patients with pancreatic cancer: a systematic review and meta-analysis. HPB (Oxford). 2019;21(12):1603-1612

27. Kamarajah SK, Chapman SJ, Glasbey J, Morton D, Smart N, Pinkney T, et al. Systematic review of the stage of innovation of biological mesh for complex or contaminated abdominal wall closure. BJS Open. 2018;2(6):371-380.

28. Hsu PK, Chen HS, Wu SC, Wang BY, Liu CY, Shih CH, et al. Impact of hospital volume on long-term survival after resection for oesophageal cancer: a population-based study in Taiwandagger. Eur J Cardiothorac Surg. 2014;46(6):e127-35; discussion e35.

29. Varagunam M, Hardwick R, Riley S, Chadwick G, Cromwell DA, Groene O. Changes in volume, clinical practice and outcome after reorganisation of oesophago-gastric cancer care in England: A longitudinal observational study. Eur J Surg Oncol. 2018;44(4):524-531.

30. Hulscher JB, van Sandick JW, de Boer AG, Wijnhoven BP, Tijssen JG, Fockens P, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med. 2002;347(21):1662-1669.

31. Omloo JM, Lagarde SM, Hulscher JB, Reitsma JB, Fockens P, van Dekken H, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. Ann Surg. 2007;246(6):992-1000; discussion -1.

32. Law S, Fok M, Chu KM, Wong J. Comparison of hand-sewn and stapled esophagogastric anastomosis after esophageal resection for cancer: a prospective randomized controlled trial. Ann Surg. 1997;226(2):169-173.

33. Gooszen JAH, Goense L, Gisbertz SS, Ruurda JP, van Hillegersberg R, van Berge Henegouwen MI. Intrathoracic versus cervical anastomosis and predictors of anastomotic leakage after oesophagectomy for cancer. Br J Surg. 2018;105(5):552-560.

34. Liu YJ, Fan J, He HH, Zhu SS, Chen QL, Cao RH. Anastomotic leakage after intrathoracic versus cervical oesophagogastric anastomosis for oesophageal carcinoma in Chinese population: a retrospective cohort study. BMJ Open. 2018;8(9):e021025.

35. Akiyama S, Kodera Y, Sekiguchi H, Kasai Y, Kondo K, Ito K, et al. Preoperative embolization therapy for esophageal operation. Journal of Surgical Oncology. 1998;69(4):219-223.

36. Pham TH, Melton SD, McLaren PJ, Mokdad AA, Huerta S, Wang DH, et al. Laparoscopic ischemic conditioning of the stomach increases neovascularization of

the gastric conduit in patients undergoing esophagectomy for cancer. J Surg Oncol. 2017;116(3):391-397.

37. Bludau M, Hölscher AH, Vallböhmer D, Gutschow C, Schröder W. Ischemic Conditioning of the Gastric Conduit Prior to Esophagectomy Improves Mucosal Oxygen Saturation. The Annals of Thoracic Surgery. 2010;90(4):1121-1126.

38. Perry KA, Banarjee A, Liu J, Shah N, Wendling MR, Melvin WS. Gastric ischemic conditioning increases neovascularization and reduces inflammation and fibrosis during gastroesophageal anastomotic healing. Surg Endosc. 2013;27(3):753-760.

39. Reavis KM, Chang EY, Hunter JG, Jobe BA. Utilization of the delay phenomenon improves blood flow and reduces collagen deposition in esophagogastric anastomoses. Ann Surg. 2005;241(5):736-745; discussion 45-7.

40. Wajed SA, Veeramootoo D, Shore AC. Video. Surgical optimisation of the gastric conduit for minimally invasive oesophagectomy. Surg Endosc. 2012;26(1):271-276.

41. Perry KA, Enestvedt CK, Pham TH, Dolan JP, Hunter JG. Esophageal replacement following gastric devascularization is safe, feasible, and may decrease anastomotic complications. J Gastrointest Surg. 2010;14(7):1069-1073.

42. Alderson D. Scottish Intercollegiate Guidelines Network (SIGN) 87--the management of oesophageal and gastric cancer. Clin Oncol (R Coll Radiol). 2008;20(7):530-531.

43. Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R, et al. Guidelines for the management of oesophageal and gastric cancer. Gut. 2011;60(11):1449-1472.

44. Shapiro J, van Lanschot JJB, Hulshof M, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol. 2015;16(9):1090-1098.

45. Kohler H, Jansen-Winkeln B, Maktabi M, Barberio M, Takoh J, Holfert N, et al. Evaluation of hyperspectral imaging (HSI) for the measurement of ischemic conditioning effects of the gastric conduit during esophagectomy. Surg Endosc. 2019;33(11):3775-3782.

46. Prudius V, Procházka V, Pavlovský Z, Peštál A, Vlček P, Čapov I, et al. Neovascularization after ischemic conditioning of the stomach and the influence of follow-up neoadjuvant chemotherapy thereon. Videosurgery and Other Miniinvasive Techniques. 2018;13(3):299-305.

47. Veeramootoo D, Shore AC, Shields B, Krishnadas R, Cooper M, Berrisford RG, et al. Ischemic conditioning shows a time-dependant influence on the fate of the gastric conduit after minimally invasive esophagectomy. Surgical Endoscopy. 2009;24(5):1126-1131.

48. Diana M, Hübner M, Vuilleumier H, Bize P, Denys A, Demartines N, et al. Redistribution of Gastric Blood Flow by Embolization of Gastric Arteries Before Esophagectomy. The Annals of Thoracic Surgery. 2011;91(5):1546-1551.

49. Farran L, Miro M, Alba E, Bettonica C, Aranda H, Galan M, et al. Preoperative gastric conditioning in cervical gastroplasty. Diseases of the Esophagus. 2010;24(4):205-210.

50. Ghelfi J, Brichon P-Y, Frandon J, Boussat B, Bricault I, Ferretti G, et al. Ischemic Gastric Conditioning by Preoperative Arterial Embolization Before

Oncologic Esophagectomy: A Single-Center Experience. CardioVascular and Interventional Radiology. 2017;40(5):712-720.

51. Holscher AH, Schneider PM, Gutschow C, Schroder W. Laparoscopic ischemic conditioning of the stomach for esophageal replacement. Ann Surg. 2007;245(2):241-246.

52. Isomura T, Itoh S, Endo T, Akiyama S, Maruyama K, Ishiguchi T, et al. Efficacy of gastric blood supply redistribution by transarterial embolization: Preoperative procedure to prevent postoperative anastomotic leaks following esophagoplasty for esophageal carcinoma. CardioVascular and Interventional Radiology. 1999;22(2):119-123.

53. Nguyen NT, Nguyen XM, Reavis KM, Elliott C, Masoomi H, Stamos MJ. Minimally invasive esophagectomy with and without gastric ischemic conditioning. Surg Endosc. 2012;26(6):1637-1641.

54. Prochazka V, Marek F, Kunovsky L, Svaton R, Grolich T, Moravcik P, et al. Comparison of cervical anastomotic leak and stenosis after oesophagectomy for carcinoma according to the interval of the stomach ischaemic conditioning. The Annals of The Royal College of Surgeons of England. 2018;100(7):509-514.

55. Siegal SR, Parmar AD, Haisley KR, Tieu BH, Schipper PH, Hunter JG, et al. Gastric Ischemic Conditioning Prior to Esophagectomy Is Associated with Decreased Stricture Rate and Overall Anastomotic Complications. Journal of Gastrointestinal Surgery. 2018;22(9):1501-1507.

56. Yetasook AK, Leung D, Howington JA, Talamonti MS, Zhao J, Carbray JM, et al. Laparoscopic ischemic conditioning of the stomach prior to esophagectomy. Dis Esophagus. 2013;26(5):479-486.

57. Veeramootoo D, Shore AC, Wajed SA. Randomized controlled trial of laparoscopic gastric ischemic conditioning prior to minimally invasive esophagectomy, the LOGIC trial. Surgical Endoscopy. 2012;26(7):1822-1829.

58. Köhler H, Jansen-Winkeln B, Maktabi M, Barberio M, Takoh J, Holfert N, et al. Evaluation of hyperspectral imaging (HSI) for the measurement of ischemic conditioning effects of the gastric conduit during esophagectomy. Surgical Endosc. 2019; 33(11):3775-3782

59. Hölscher AH. Re: Laparoscopic Ischemic Conditioning of the Stomach for Esophageal Replacement. Ann Surg. 2008;247(2):398-399.

Table 1 Characteristics of Included Studies

Study Name	Study Design	Study Country	Study Duration	Comparative	Number, n	GIC, n	No GIC, n	Method of GIC	GIC Waiting Times, days
Bludau 2010(37)	PCS	Germany	August 2006 - June 2008	None	19	19		Ligation: LGA, Short gastric arteries	4-5 days
Kohler 2019(45)	PCS	Germany	NR	GIC vs No GIC	22	14	8	Ligation: LGA, LGV	3 - 7 days
Prudius 2018(46)	PCS	Czech Republic	NR	GIC vs No GIC	15	8	7	Ligation: LGA	NR
Veeramootoo 2009(47)	PCS	United Kingdom	April 2004 - August 2008	GIC vs No GIC	97	42	55	Ligation: LGA	5 or 14
Akiyama 1998(35)	RCS	Japan	NR	GIC vs No GIC	79	54	25	Embolisation: RGA, LGA, Splenic artery	NR
Berrisford 2009(15)	RCS	United Kingdom	April 2004 - June 2007	GIC vs No GIC	77	22	55	Ligation: LGA, LGV	16
Diana 2011(48)	RCS	Switzerland	2000 - 2009	GIC vs No GIC	57	19	38	Embolisation: LGA, Splenic artery	17
Farran 2010(49)	RCS	Spain	January 2001 - December 2007	None	39	39		Embolisation: LGA, Splenic artery	14 - 21
Ghelfi 2016(50)	RCS	Germany	March 2008 - January 2015	GIC vs No GIC	59	46	13	Embolisation: LGA, RGA, Splenic artery	30
Holscher 2007(51)	RCS	Germany	December 2003 - September 2005	None	83	83		Ligation: LGA, LGV	4
Isomura 1999(52)	RCS	Japan	January 1993 - December 1995	None	37	34		Embolisation: RGA, LGA, Splenic artery	14
Nguyen 2011(53)	RCS	USA	NR	GIC vs No GIC	152	81	71	Ligation: LGA, Short gastric arteries	6
Pham 2017(36)	RCS	USA	July 2008 - January 2014	GIC vs No GIC	30	21	9	Ligation: LGA, Short gastric arteries	121
Prochazka 2018(54)	RCS	Czech Republic	January 2012 - June 2014	None	33	33		Ligation: LGA	20 or 49
Schroder 2010(16)	RCS	Germany	June 1996 - April 2008	GIC vs No GIC	419	238	181	NR	4-5 days
Siegal 2019(55)	RCS	USA	January 2010 - December 2015	GIC vs No GIC	207	38	169	Ligation: LGA, Short gastric arteries	98 days
Wajed 2012(40)	RCS	United Kingdom	April 2004 - January 2010	GIC vs No GIC	131	67	64	Ligation: LGA	14
Yetasook 2013(56)	RCS	USA	October 2008 - July 2011	None	24	24		Ligation: LGA, Short gastric arteries	NR
Veeramootoo 2012(57)	RCT	United Kingdom	NR	GIC vs No GIC	16	8	8	Ligation: LGA	NR

Abbreviations: GIC - Gastric ischaemic conditioning; LGA - left gastric artery; LGV - left gastric vein; NR - Not reported; PCS - prospective cohort study; RCS - retrospective cohort study; RCT - randomised controlled trial; RGA - right gastric artery; USA - United States of America

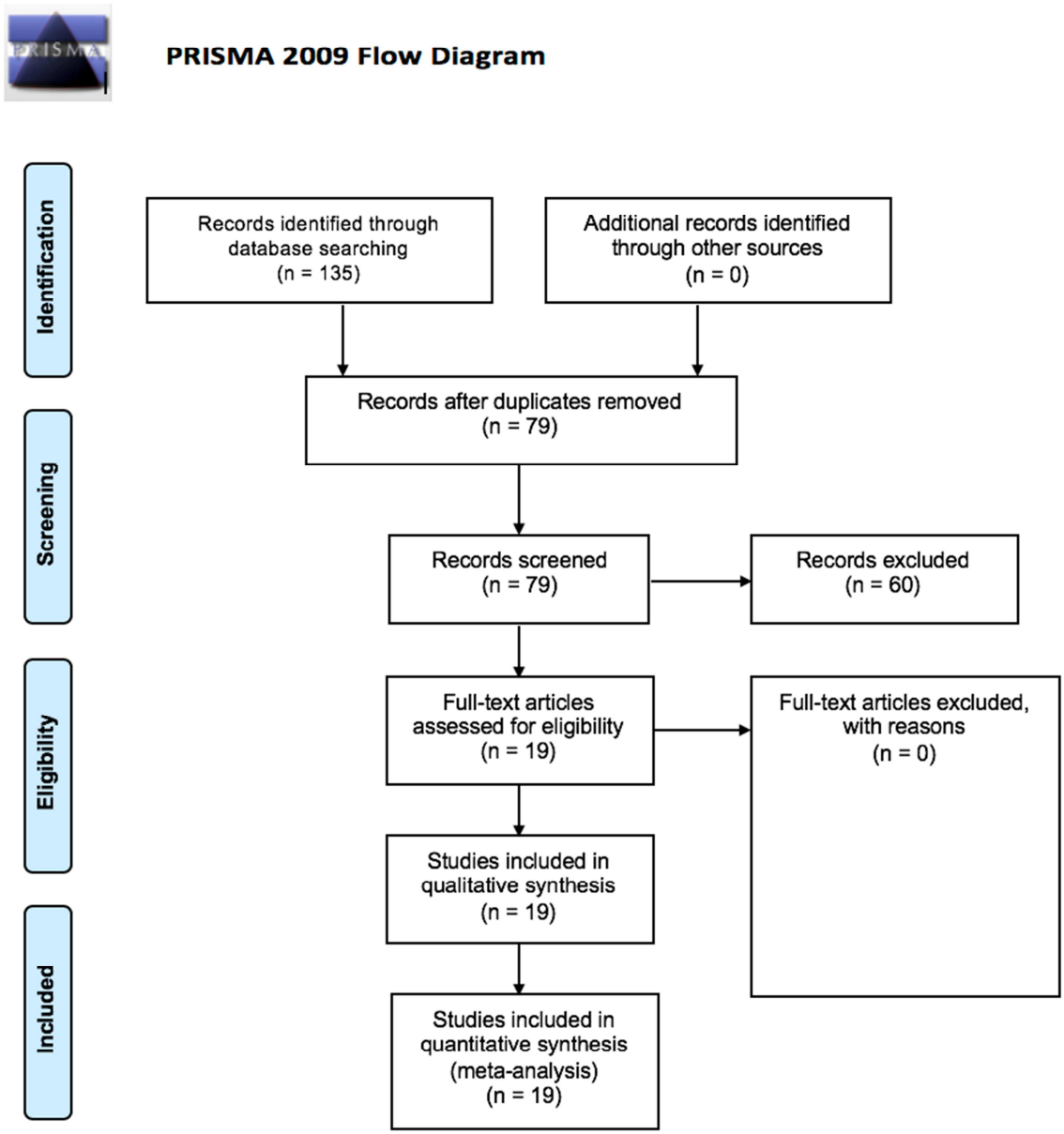
			Indication		Neoadjuvant Therapy		T Stage 3/4, n	Overall Stage 3/4, n	MIO, n
Study Name	**Age, years**	**Male, n**	**Cancer, n**	**Benign, n**	**GIC, n**	**No GIC, n**			
Bludau 2010(37)	61	17	19	0	13	-	NR	NR	NR
Kohler 2019(58)	NR	20	21	1	14	6	NR	NR	0
Prudius 2018(46)	NR	NR	15	0	4	0	NR	NR	NR
Veeramootoo 2009(47)	68	78	97	0	NR	NR	NR	NR	97
Akiyama 1998(35)	62	68	NR	NR	22	6	NR	NR	0
Berrisford 2009(15)	69	67	NR	NR	NR	NR	NR	77	77
Diana 2011(48)	64	46	57	0	5	11	NR	NR	NR
Farran 2010(49)	59.8 (9.3)	32	20	19	NR	-	NR	NR	0
Ghelfi 2016(50)	63	43	59	0	31	5	NR	18	0
Holscher 2007(51)	62	68	83	0	42	-	NR	38	0
Isomura 1999(52)	59	28	37	0	NR	-	NR	NR	NR
Nguyen 2011(53)	65	118	134	18	23	36	NR	NR	152
Pham 2017(36)	64	27	30	0	20	5	NR	11	30
Prochazka 2018(54)	61	30	33	0	33	-	NR	12	33
Schroder 2010(16)	60 (18 - 81)	349	419	0	144	66	183	NR	0
Siegal 2019(55)	65	172	194	13	36	120	NR	96	196
Wajed 2012(40)	67	109	131	0	NR	NR	NR	NR	131
Yetasook 2013(56)	62 (8)	19	24	0	21	-	NR	21	0
Veeramootoo 2012(57)	NR	NR	16	0	NR	NR	NR	NR	16

Table 2 Baseline Demographics of Included studies

Table 3 Summary of postoperative outcomes of gastric ischaemic conditioning

Outcomes	Studies, n	OR (CI95%)	p-value	I^2
Anastomotic Leaks				
Overall	11	0.7973 [0.5115; 1.2428]	0.3	8
Ligation	7	1.2616 [0.6945; 2.2919]	0.4	0
Embolisation	3	0.2494 [0.0939; 0.6620]	**0.005**	0
Conduit Necrosis				
Overall	4	0.2977 [0.1149; 0.7710]	**0.013**	0
Ligation	4	0.2977 [0.1149; 0.7710]	**0.013**	0
Embolisation	0	-	-	-
Anastomotic Stricture				
Overall	5	0.7476 [0.3478; 1.6069]	0.5	20
Ligation	3	0.6496 [0.1834; 2.3007]	0.5	57
Embolisation	2	0.7320 [0.1466; 3.6541]	0.7	0
Overall Complications				
Overall	5	1.0168 [0.4785; 2.1610]	0.9	55
Ligation	4	0.8902 [0.3810; 2.0799]	0.8	62
Embolisation	1	-		
Major Complications				
Overall	3	1.0588 [0.5311; 2.1108]	0.9	0
Ligation	2	0.8976 [0.2471; 3.2604]	0.9	16
Embolisation	1	-		
Pulmonary Complications				
Overall	5	0.8960 [0.5684; 1.4126]	0.6	0
Ligation	2	0.9015 [0.4071; 1.9962]	0.8	24
Embolisation	2	1.3535 [0.5689; 3.2203]	0.5	0
In-hospital mortality				
Overall	7	0.6989 [0.3191; 1.5304]	0.4	21
Ligation	4	1.4411 [0.5313; 3.9088]	0.5	0
Embolisation	2	0.2656 [0.0207; 3.4119]	0.3	55

Figure 1 PRISMA Diagram of included studies



Supplementary Table 1 Summary of terms for literature search

1	Gastric ischemic conditioning.ti,ab.	29
2	ischemic conditioning.ti,ab.	1123
3	Gastric Ischemic Preconditioning.ti,ab.	27
4	Laparoscopic Conditioning.ti,ab.	4
5	Conditioning.ti,ab.	204966
6	1 or 2 or 3 or 4 or 5	204988
7	oesophagectomy.ti,ab.	4378
8	esophagectomy.ti,ab.	23837
9	exp Esophagectomy/	28826
10	7 or 8 or 9	38114
11	6 and 10	129

Supplementary Table 2 Summary of quality assessment of study quality

	Selection	Comparability	Outcome	Overall
Bludau 2010(37)	-	-	-	Non-Comparative
Kohler 2019(58)	2	0	3	5
Prudius 2018(46)	3	0	3	6
Veeramootoo 2009(47)	4	0	3	7
Akiyama 1998(35)	3	0	3	6
Berrisford 2009(15)	4	0	3	7
Diana 2011(48)	3	2	3	8
Farran 2010(49)	-	-	-	Non-Comparative
Ghelfi 2016(50)	3	2	3	8
Holscher 2007(59)	-	-	-	Non-Comparative
Isomura 1999(52)	-	-	-	Non-Comparative
Nguyen 2011(53)	4	0	3	7
Pham 2017(36)	4	0	3	7
Prochazka 2018(54)	-	-	-	Non-Comparative
Schroder 2010(16)	3	0	3	6
Siegal 2019(55)	2	0	3	5
Wajed 2012(40)	3	0	3	6
Yetasook 2013(56)	-	-	-	Non-Comparative

Critical Appraisal of Gastric Conduit Ischaemic Conditioning (GIC) prior to Oesophagectomy: A Systematic Review and Meta-Analysis

1. Nineteen studies reported on GIC, of which 13 were comparative studies.
2. GIC did not appear to reduce anastomotic leakages (OR 0.80, $CI_{95:}$ 0.51 - 1.24, p=0.3) and anastomotic strictures (OR 0.75, $CI_{95:}$ 0.35 - 1.60, p=0.5)
3. However, GIC was associated with reduced rates of conduit necrosis (OR 0.30, $CI_{95:}$ 0.11 - 0.77, p=0.013)

The data has been extracted from all referenced studies for this meta-analysis.

International Journal of Surgery Author Disclosure Form

The following additional information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories then this should be stated.

Please state any conflicts of interest

None

Please state any sources of funding for your research

None

Please state whether Ethical Approval was given, by whom and the relevant Judgement's reference number

Not Applicable

Research Registration Unique Identifying Number (UIN)

Please enter the name of the registry and the unique identifying number of the study. You can register your research at http://www.researchregistry.com to obtain your UIN if you have not already registered your study. This is mandatory for human studies only.

PROSPERO 2019
CRD42019137432
Available from:
https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019137432

Author contribution

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis, writing. Others, who have contributed in other ways should be listed as contributors.

Study design - SKK, BT
Data Collection - SKK, CB, JRB
Data Analysis - SKK, BT
Writing - SKK, BT

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Sivesh K Kamarajah