Interventions to Prevent Anastomotic Leak After Esophageal Surgery: A Systematic Review and Meta-Analysis

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Abstract

Background:

Anastomotic leakage (AL) is a common and serious complication following esophagectomy. We aimed to provide an up-to-date review and critical appraisal of interventions designed to reduce AL risk.

Methods:

We searched MEDLINE and Embase from 1946 to January 2019 for randomized controlled trials (RCTs) evaluating interventions to minimize esophagogastric AL. Pooled risk ratios (RR) for AL was performed using random effects.

Results:

Two reviewers screened 441 abstracts and identified 17 RCTs eligible for inclusion; 11 studies were meta-analyzed. Omentoplasty reduced the risk of AL significantly by 78% [RR: 0.22; 95% CI: 0.10, 0.50] compared to no omentoplasty (3 studies, n=611 patients). Early removal of NG tube reduced AL risk significantly by 88% [RR: 0.12; 95% CI: 0.02, 0.65] compared to prolonged NG tube (2 studies, n=293 patients); Stapled (vs. hand-sewn) anastomosis did not significantly reduce AL risk [RR: 0.92; 95% CI: 0.45, 1.87] compared to hand-sewn (6 studies, n=1454 patients). The quality of evidence was high for omentoplasty (vs. no omentoplasty), moderate for early removal of NG tube (vs. conventional removal), and very low for stapled anastomosis (vs. hand-sewn).

Conclusions:

This is the first meta-analysis to summarize the graded quality of evidence for all RCT interventions designed to reduce AL following esophagectomy. Our findings demonstrated that omentoplasty reduced the risk of AL with a high quality of evidence. Although early nasogastric tube removal reduced AL risk, there is a need for further research to strengthen the quality of evidence. Evidence profiles presented in our review may help inform the development of clinical practice recommendations.

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Background

Esophagectomy is a critical component of curative treatment for esophageal cancer. This procedure carries a significant risk for certain adverse events among patients undergoing esophagectomy. One of the most serious adverse events associated with esophagectomy is an anastomotic leak, which involves the leak of gastric fluid outside of the anastomosis post-operatively [1]. The presence of anastomotic leakage, with the rates being shown to occur up to 50% in some studies, is a potentially serious adverse event for patients and it has previously been significantly associated with prolonged length of stay, the formation of strictures, and increased morbidity and mortality [2, 3].

There have been several interventions conducted previously that aimed to prevent AL, ranging from surgical interventions to more conservative measures. Omentoplasty is a standardized surgical technique that harnesses a pedicle flap from the omentum (a layer of abdominal fat that is attached to the greater curvature of the stomach) to cover or wrap around the anastomosis site. The omental flap, secured in place with hand-sewn sutures, is well perfused by vascularity from the preserved left gastro-epiploic artery [4, 5, 6]. Thus, the good vascularity the omental flap provides to the surgical site, including oxygen and nutrient-rich blood, is thought to enhance wound healing [7]. Omentoplasty after an esophagectomy has demonstrated promising findings in previous RCTs to prevent AL post-operatively, which has been summarized in a meta-analysis conducted six years ago by Chen et al. in 2014 and Yuan et al 2019 [8, 9]. Another intervention investigated previously in the literature includes the early removal of the nasogastric (NG) tube after surgery. The strain on the wall of the esophagus when the anastomotic site is dilated is thought to lead to poor vascular perfusion of the surgical site, which may increase the risk for anastomotic leakage; NG decompression, which reduces dilation of the tissue, may reduce the risk for an anastomotic leak [11]. Weijs et al. in 2017 meta-analyzed previous controlled trials and reported that the early removal of NG tubes did not significantly alter the rates of AL compared to standard NG tube use after esophagectomy [12]. Other studies have explored the potential for administering different anastomotic surgical techniques to prevent of AL [11]. A meta-analysis by Beitler et al. compared the rates of AL according to the use of hand-sewn vs. stapled anastomoses but found no difference among groups that used hand-sewn vs. stapled anastomoses [10]. An up-to-date summary of the literature is warranted to consider more recently published literature.

There is a need for an up-to-date review comparing the efficacy of all previous interventions designed to prevent AL after esophagectomy. A systematic approach to grading the quality, which can be accomplished using frameworks such as GRADE (Grading of Recommendations, Assessment, Development, and Evaluations), is essential to guide clinical practice recommendations [17]. Therefore, the present meta-analysis aims to provide a comprehensive and up-to-date summary of all previous interventional randomized controlled trials that aimed to reduce esophagogastric anastomotic leakage rates after esophagectomy and conduct a systematic grading of quality among interventions meta-analyzed.

Methods

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (PRISMA checklist) [37]. The protocol is available in the International Prospective Register of Systematic Reviews (CRD42019127181).

Search strategy

MEDLINE (OVID interface, including In-process and Epub Ahead of Print) and Embase (OVID interface) databases were searched from 1946 to February 2019 (supplemental 1). The literature search results were uploaded and reviewed using Covidence Software (Covidence, Melbourne, Australia).

Selection criteria

Search results and full-text articles meeting full eligibility criteria were reviewed independently and in duplicate. Potentially relevant studies were screened by title and abstract (stage 1) followed by full-text article screening to assess full eligibility (stage 2). Two review authors assessed the eligibility of full reports. Any disagreement was resolved through discussion with a third reviewer. The reasons for excluding studies were recorded. RCTs that evaluated any intervention to minimize AL following esophagectomy were included with no restriction on language. Only studies that reported our primary outcome, AL, were included. Properly conducted RCTs are the gold standard for evaluating the effectiveness of an intervention [13]. Thus, only RCT articles were included and other articles, including review articles, editorials, preclinical studies, observational studies, and abstracts, were excluded.

Outcome justification and prioritization

Our primary outcome of interest was an anastomotic leak, required to be recorded for both interventional and control groups. AL was defined as the presence of extraluminal collections of air or contrast, excess bile-stained fluid on drainage, or a combination of these [13]. Secondary outcomes of interest were anastomotic stricture, mortality, and length of stay in hospital post-operatively.

Data extraction

Patient characteristics and demographic information, methodology, intervention details, outcomes of interest, and risk of bias were recorded. Two reviewers performed all data extraction. The study and patient characteristics for included studies were recorded. This included the first author name, year of publication, study country of origin, number of patients investigated (intervention and control groups), and the indication for esophagectomy (e.g. esophageal cancer). The methods used for interventions to prevent AL were recorded (e.g. omentoplasty, stapled vs. hand-sewn anastomosis, early NG tube removal. Details recorded included the use of neoadjuvant therapy (e.g. radiation and chemotherapy), medical management (e.g. antibiotics), endoscopic management (e.g. nasogastric tube use), or surgical management (e.g. re-operation), the modality used to diagnosis AL, and the surgical approach for esophagogastric anastomosis (e.g. cervical or thoracic anastomosis). Disagreements were resolved through discussion with a third-party member.

Summary measures and synthesis of results

DerSimonian and Laird's random-effects method was used to pool relative risk effect estimates with corresponding 95% CIs for dichotomous variables. A risk ratio of greater than one indicates an increased risk of AL, stricture, or mortality and less than one indicates a reduced risk of AL, stricture, or mortality. Continuous measures were reported for individual studies as a mean with standard deviation (SD) or a median with interquartile range (IQR) or the overall range from minimum to maximum. The pooled mean difference between the length of stay in the intervention and control groups was determined using a DerSimonian and Laird's random-continuous effects method [15]. Studies that reported median with IQR were excluded from the pooled mean difference estimation for the length of stay. A mean difference in length of stay less than zero represents a shorter length of stay in the intervention group compared to the control group and a value greater than zero represents a longer length of stay in hospital in the intervention group compared to the control group. The heterogeneity of effect sizes for pooled estimates was assessed using the Cochrane I^2 statistic. The following thresholds were used to describe the I^2 threshold: 0 – 40% (low heterogeneity), 30 – 60% (moderate heterogeneity), 50 – 90% (substantial heterogeneity) and 75 – 100% (considerable heterogeneity) [15]. Open Meta-Analyst was used to generate forest plots, heterogeneity, and effect estimates for risk ratios and mean differences (Open-source, USA).

Subgroup analyses included analyzing AL grouped by type of disease (e.g. esophageal cancer), age (≤ or > 18 years old), type of surgery (cervical vs. thoracic anastomosis), and use of induction or neoadjuvant therapy.

Risk of Bias

The Cochrane revised risk of bias tool for randomized trials was used to evaluate the individual risk of bias for studies reviewed [17]. Within each risk of bias domain, a series of questions ('signaling questions') were chosen to elicit information about features of the trial that were felt to be relevant to the risk of bias. Publication bias was included in the assessment. Judgement is classified as 'low', 'high', or as having 'some concerns' [17]. Meta-bias (risk of bias across studies) was summarized by pooling the individual study risk of bias for each risk of bias domain.

Grading of Recommendations, Assessment, Development, and Evaluations

The quality of the treatment effects was graded by using a systematic and comprehensive approach known as GRADE [17]. GRADE provides a reproducible and transparent framework for grading the quality of evidence or certainty in the evidence. The quality of evidence reflects the extent to which we are confident that an estimate of the effect is correct. High grade of evidence means the true estimate lies close to the estimate of effect; moderate grade means that the true effect is likely to be close to the estimate of the effect; low grade means that the effect estimate may substantially differ from the true estimate of the effect; very low grade means we have little confidence in the effect estimate [17].

Results

The systematic searches returned a total of 731 citations. Following deduplication, 441 citations were identified. Of the 441 citations, 73 full manuscripts were identified as potentially eligible with a total of 17 RCTs meeting our eligibility criteria (n = 3,157 participants). Eleven studies were included in our meta-analysis as shown in our PRISMA flow diagram (**Figure 1**).

Studies were published between 1996 and 2019, with sample sizes ranging from 32 to 516 participants. The mean age of participants was similar across studies ranging from 50.8 to 67.5 years old. Follow-up periods were highly variable ranging from 3 months to 3 years. Most studies were performed in China (5 studies, 19%), India (4 studies, 24%), or Japan (3 studies, 18%). The number of male participants was higher than female participants in all studies except one. The incidence of AL ranged from 1.4 to 17%. The patient characteristics of the included studies are provided in **Table 1**.

Seven studies (41%) investigated stapled (vs. hand sewn) anastomosis, three studies (18%) investigated omentoplasty (vs. hand-sewn or stapled) anastomosis, three studies (18%) investigated early removal (post-op day 1 or 2 days) or no nasogastric tube (vs. conventional 7 to 10 days to nasogastric tube removal), two studies (12%) that investigated subtotal gastric resection (vs. slender gastric tube) reconstruction, one study (6%) investigated valvuloplasty (vs. stapled) anastomosis, and one study (6%) that compared end-to-end (vs. end-to-side) anastomosis. Sixteen studies (94%) used contrast to diagnose AL and six studies (35%) used additional endoscopy and/or chest tube or drain output. Seven studies (41%) administered medical management, three studies (18%) administered surgical management, and two studies (12%) administered endoscopic management for the treatment of AL. The length of stay in hospital post-operatively varied from 10.7 to 29.4 days. The study intervention characteristics are outlined in **Table 2**.

Primary Outcome

Anastomotic leakage

The pooled results for 11 meta-analyzed studies are summarized in **Figure 2** and the descriptive results for single RCT interventions are summarized in **Supplemental 2**. Esophagectomy patients that received stapled esophagogastric anastomosis demonstrated a similar reduction in risk of AL (RR: 0.92; 95% CI: 0.45, 1.87; I^2 40.1%) compared to hand-sewn (6 studies, n = 1,454). Esophagectomy patients that received omentoplasty had a significant 78% lower risk of leakage (RR: 0.22; 95% CI: 0.10, 0.50; I^2 0%) compared to hand-sewn or stapled anastomosis alone (3 studies, n = 611 patients). Esophagectomy patients with early removal or no nasogastric tube demonstrated a significant 88% reduction in risk of leakage (RR: 0.12; 95% CI: 0.02, 0.65; I^2 0%) compared to prolonged nasogastric tube removal (2 studies, n = 293 patients).

The pooled risk ratios (RR) for AL were sub-grouped according to the site of esophagogastric anastomosis among 2 studies (**Table 3**). The pooled risk ratio for esophagectomy patients grouped according to cervical esophagogastric anastomosis (2 studies, RR: 0.23; 95% CI: 0.069, 0.788; I^2 0%) was similar to the pooled RR for thoracic esophagogastric anastomosis (2 studies, RR: 0.19; 95% CI: 0.034, 1.032; I^2 0%). The pooled risk ratios (RR) for AL among omentoplasty patients were also sub-grouped according to whether comparison groups received a stapled or hand-sewn anastomosis (refer Supplemental 3). The risk ratio for patients in the stapled anastomosis study (n = 1 study, RR: 0.214; 95% CI: 0.064, 0.722) was similar to the pooled risk of AL for patients in the hand-sewn anastomosis studies (n = 2 studies, RR: 0.264; 95% CI: 0.089, 0.789). Due to a lack of reporting of AL according to neoadjuvant therapy type (radiation and/or chemotherapy), it was not possible to conduct a stratified analysis.

Secondary Outcomes

Anastomotic stricture

Esophagectomy patients that received stapled esophagogastric anastomosis had a 2-fold increased risk of stricture (RR: 2.11; 95% CI: 1.36, 3.26; I^2 35.0%) compared to hand-sewn esophagogastric anastomosis (6 studies, n = 1,380). Esophagectomy patients that received omentoplasty had an 8% lower and not significantly different risk of stricture (RR: 0.92; 95% CI: 0.33, 2.57; I^2 65.1%) compared to no omentoplasty (3 studies, n = 613 patients). The pooled results are summarized in **Figure 3**.

Mortality rate

Esophagectomy patients that received stapled esophagogastric anastomosis had no statistically significant difference in risk of mortality (RR: 1.22; 95% CI: 0.75, 1.98; I^2 0%) compared to hand-sewn esophagogastric anastomosis (6 studies, n =1363). Esophagectomy patients that received omentoplasty had a 20% lower risk of mortality (RR: 0.80; 95% CI: 0.32, 2.0; I^2 0%) compared to no omentoplasty (3 studies, n = 736 patients). Esophagectomy patients with early removal or no nasogastric tube demonstrated no statistically significant difference in risk of mortality (RR: 0.90; 95% CI: 0.317, 2.55; I^2 0%) compared to prolonged nasogastric tube removal (2 studies, n =190 patients). The pooled results are summarized in **Figure 4**.

Length of Stay

The weighted mean difference (WMD) in the post-operative length of stay in hospital was determined based on the mean (SD) reported among the included studies. Esophagectomy patients that received stapled anastomosis did not have a significantly different mean length of stay in hospital with a stay of 1.1 days longer [95% CI: -0.01, 2.2; I^2 0%] compared to hand-sewn (2 studies, n = 606). Esophagectomy patients that received omentoplasty had a statistically significant 2.1 day shorter mean length of stay in hospital (WMD: -2.1; 95% CI: -3.6, -0.6; I^2 0%) compared hand-sewn or stapled anastomosis alone (2 studies, n = 417 patients). Esophagectomy patients with early removal or no nasogastric tube demonstrated a non-significant 3.2 day shorter mean length of stay in hospital (WMD: -3.2; 95% CI: -6.5, 0.2; I^2 0%) compared to prolonged nasogastric tube removal (2 studies, n = 111 patients). Mistry *et al.* 2012 was excluded from the pooled WMD estimate as the investigators reported a median (IQR). Mistry *et al.* 2012 reported that the early removal or no nasogastric tube and prolonged nasogastric tube removal groups both had a length of stay of 12 with no statistically significant difference (P=0.18) [26].

Risk of Bias

Seven (64%) meta-analyzed studies did not report whether the allocation of participants was concealed. Nine (82%) meta-analyzed studies lacked any details surrounding blinding of outcome assessment was blinded. Ten (91%) meta-analyzed studies lacked reporting of outcome assessment blinding. The risk of bias results are summarized in **Figure 5** (refer to **Supplemental 4**).

Grade

There was a high quality of evidence for AL in the omentoplasty intervention. The unclear risk of bias in omentoplasty studies was due to the lack of allocation concealment in one study decreased the quality of evidence by one level. The large magnitude of effect in the omentoplasty studies increased the quality of evidence by one level. There was a moderate quality of evidence for AL in the early removal or no nasogastric tube intervention. The high risk of bias due to both the lack of randomization and allocation concealment in all studies decreased the quality of evidence by two levels. The large magnitude of effect increased the quality of evidence by one level. There was a very low quality of evidence for AL in the stapled anastomosis intervention. The high risk of bias due to both the lack of randomization and allocation concealment in nearly all studies decreased the quality of evidence by two levels. The imprecision of the measure of effect due to the lack of statistical significance reduced the quality of evidence by one level. The moderate level of heterogeneity in the pooled estimate decreased the quality of evidence by one level. The evidence profile is summarized according to intervention type in Table 3 (refer to Supplemental 5).

Discussion

This is the first systematic review and meta-analysis to provide graded quality of evidence for all previous RCTs investigating interventions to reduce anastomotic leakage (AL) following esophagectomy. Our review suggests there is a high quality of evidence that omentoplasty significantly reduces the risk of AL. The mechanism of benefit (improved perfusion to the surgical site) that omentoplasty has on wound healing may offer further justification to the high quality of evidence supporting this significant reduction in risk of AL [21, 34–35]. Our findings showed that omentoplasty not only reduced AL, but also lowered the risk of anastomotic stricture, mortality, and mean length of stay in hospital following esophageal cancer resection; However, this finding was not statistically significant in anastomotic stricture or mortality. The early removal or no nasogastric tube intervention showed a substantial reduction in the risk of AL when compared to prolonged nasogastric tube removal; however, the moderate quality of evidence for this intervention indicates the need for further research. There was a small difference in risk of AL for stapled vs. hand-sewn anastomosis, but it was not significant. The quality of evidence for stapled (vs. hand-sewn) anastomosis was very low.

In the present meta-analyses, subgroup group analysis based on the location of anastomosis revealed that there was a less protective effect of omentoplasty to prevent AL in the cervical esophagogastric anastomosis groups; This finding should be interpreted with caution due to the low number of omentoplasty studies sub-grouped (n = 2 studies). The finding that esophagogastric anastomosis location has some association with the presence of anastomotic leak is consistent with previous literature. Many studies have shown that there are higher rates of AL in patients who undergo transhiatal surgery compared to transthoracic. However, the possible mechanism(s) explaining differences in AL rates based on location remains somewhat controversial [4, 19]. Some studies have attempted to better elucidate the underlying mechanisms. In two previous meta-analyses, the rates of AL in patients that had transhiatal esophagectomy (use of cervical anastomosis) were significantly higher compared to patients that had transthoracic or Ivor Lewis esophagectomy (use of thoracic anastomosis) [33, 34]. Other literature has hypothesized that the differences in AL rates based on cervical and thoracic locations may be due to perfusion issues of the gastric conduit reaching the neck. The latter is supported by the well-established understanding that perfusion and oxygen delivery to the site of wound healing after surgical resection has a substantial influence on the integrity of the wound healing process [33–35].

There is a need for further research and improved reporting in future RCTs to allow for elucidation of possible group differences. The paucity of studies surrounding the investigation of early removal or no nasogastric tube removal, subtotal gastric reconstruction intervention vs. a slender tube, and other techniques such as valvuloplasty may reflect the need for further research to better understand the role of these interventions in the prevention of AL. Another limitation of our meta-analysis of omentoplasty studies is that the comparison group included both stapled and hand-sewn anastomosis. However, the risk of AL among omentoplasty studies was not significantly different when sub-grouped by stapled vs. hand-sewn anastomosis. Thus, we do not anticipate this limitation to influence our conclusions. Finally, we were unable to obtain data in the included studies to allow for subgroup analysis according to the presence or absence of adjuvant radiation and/or chemotherapy.

Our review identified some gaps in the literature that may be better understood with further research. The lack of reported measures of quality of life or psychometric outcomes was one area where further exploration may be beneficial. The patient-reported outcomes may allow us to better understand key aspects of patient experience to improve the quality of care around the delivery of interventions. Another barrier was the lack of RCTs performed in North America, which means that findings may not necessarily be representative of North American populations undergoing esophageal cancer treatments. It may be useful to confirm whether the findings are generalizable to North American populations.

Conclusion

Our systematic review and meta-analysis summarizes the efficacy and safety of interventions aiming to reduce anastomotic leakage following esophagectomy. Our findings demonstrated that omentoplasty reduced the risk of anastomotic leak (compared to conventional anastomosis) with a high quality of evidence. Since early nasogastric tube removal findings provided a moderate quality of evidence, further research is recommended. Future RCTs should aim to strengthen the quality of evidence for this intervention; it demonstrates promising results that are likely to be strengthened by further research. Quality of evidence profiles presented our review may help inform future guideline recommendations surrounding the role of omentoplasty in clinical practice.

Abbreviations

AL, anastomotic leak; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; IQR, interquartile range; NG, nasogastric; PRISMA, preferred reporting in systematic reviews and meta-analysis; RCT, randomized controlled trial; RR, risk ratio; TE, transesophageal; TH, transhiatal; TT, transthoracic; WMD, weighted mean difference.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated in our review are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Ms. Grigor had full access to all the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: EG, DM, AS.

Acquisition of data: EG, SK.

Analysis or interpretation of data: EG, SK, DM, AS.

Drafting of the manuscript: EG.

Critical revision of the manuscript: All authors.

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References

1. Low ED, Kuppusamy KM, Alderson CD, Cecconello BI, Chang SA, Darling MG, et al. Benchmarking Complications Associated with Esophagectomy. *Annals of Surgery* [Online]. 2019;269(2):291–8.
2. Tabatabai A, Hashemi M, Mohajeri G, Ahmadinejad M, Khan I, Haghdani S. Incidence and risk factors predisposing anastomotic leak after transhiatal esophagectomy. (Original Article)(Clinical report). *Annals of Thoracic Medicine*. [Online]. 2009;4(4):197–200.
3. Markar S, Arya R, Karthikesalingam S, Hanna A. Technical Factors that Affect Anastomotic Integrity Following Esophagectomy: Systematic Review and Meta-analysis. *Annals of Surgical Oncology* [Online]. 2013;20(13):4274–81.
4. Zheng Q, Wang J, Ying M, Liu S. Omentoplasty in preventing anastomotic leakage of oesophagogastrostomy following radical oesophagectomy with three-field lymphadenectomy. *European Journal of Cardio-Thoracic Surgery* [Online]. 2013;43(2):274–8.
5. Dai J, Zhang Z, Min J, Huang X, Wang J. Wrapping of the omental pedicle flap around esophagogastric anastomosis after esophagectomy for esophageal cancer. *Surgery* [Online]. 2011;149(3):404–10.
6. Bhat MA, Dar MA, Lone GN, Dar AM. Use of Pedicled Omentum in Esophagogastric Anastomosis for Prevention of Anastomotic Leak. The Annals of Thoracic Surgery. 2006;82.5:1857–62.
7. Liu Q, Deng X, Wang J, Hou B, Li J, Min J, et al. Use of oesophageal flap valvuloplasty and wrapping suturing technique in preventing postoperative complications after oesophagectomy for oesophageal cancer. *European Journal of Surgical Oncology* [Online]. 2014;40(10):1355–60.
8. Chen L, Liu F, Wang K, Zou W. Omentoplasty in the prevention of anastomotic leakage after oesophagectomy: A meta-analysis. *European Journal of Surgical Oncology* [Online]. 2014;40(12):1635–40.
9. 10.1002/14651858.CD008446.pub3
   Yuan Y, Zeng X, Hu Y, Xie T, Zhao Y. Omentoplasty for oesophagogastrostomy after oesophagectomy. Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD008446. DOI: 10.1002/14651858.CD008446.pub3.
10. Beitler AL, Urschel JD. Comparison of Stapled and Hand-sewn Esophagogastric Anastomoses. *The American Journal of Surgery* [Online]. 1998;175(4):337–40.
11. Vetter D, Gutschow C. Strategies to prevent anastomotic leakage after esophagectomy and gastric conduit reconstruction. Langenbeck's Archives of Surgery. 2020. https://doi.org/10.1007/s00423-020-01926-8.
12. Weijs T, Kumagai K, Berkelmans G, Nieuwenhuijzen G, Nilsson M, Luyer M. Nasogastric decompression following esophagectomy: a systematic literature review and meta-analysis. *Diseases of the Esophagus* [Online]. 2017;30(3):1–8.
13. Hariton E, Locascio J. Randomised controlled trials – the gold standard for effectiveness research. *BJOG: An International Journal of Obstetrics Gynaecology* [Online]. 2018;125(13):1716–6.
14. Persson S, Rouvelas I, Kumagai K, Song H, Lindblad M, Lundell L, et al. Treatment of esophageal anastomotic leakage with self-expanding metal stents: analysis of risk factors for treatment failure. [Online]. 2016;4(4):E420–6.
15. Fergusson D, Laupacis A, Salmi L, Mcalister F, Huet C, Fergusson D. What should be included in meta-analyses? An Exploration of Methodological Issues Using the ISPOT Meta-Analyses. *International Journal of Technology Assessment in Health Care* [Online]. 2000;16(04):1109–19.
16. Ahn E, Kang H. (2018) Introduction to systematic review and meta-analysis. *Korean journal of anesthesiology*. [Online] 71 (2), 103–112. [online]. Available from: http://search.proquest.com/docview/2022131701/.
17. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924–6.
18. 10.1
    Higgins JPT, Sterne JAC, Savović J, Page MJ, Hróbjartsson A, Boutron I, et al. (2016) A revised tool for assessing risk of bias in randomized trials In: Chandler J, McKenzie J, Boutron I, Welch V, editors. Cochrane Methods. *Cochrane Database of Systematic Reviews*. 10.1.
19. Gooszen J, Goense L, Gisbertz S, Ruurda J, Van Hillegersberg R, Van Berge Henegouwen M. Intrathoracic versus cervical anastomosis and predictors of anastomotic leakage after oesophagectomy for cancer. *British Journal of Surgery* [Online]. 2018;105(5):552–60.
20. Daryaei P, Vaghef Davari F, Mir M, Harirchi I, Salmasian H. Omission of Nasogastric Tube Application in Postoperative Care of Esophagectomy. *World Journal of Surgery* [Online]. 2009;33(4):773–7.
21. Gupta NM, Gupta RR, Manikyam S, Gupta V. Minimizing cervical esophageal anastomotic complications by a modified technique. *The American Journal of Surgery* [Online]. 2001;181(6):534–9.

22. Hayashi M, Kawakubo H, Shoji Y, Mayanagi S, Nakamura R, Suda K, et al. Analysis of the Effect of Early Versus Conventional Nasogastric Tube Removal on Postoperative Complications After Transthoracic Esophagectomy: A Single-Center, Randomized Controlled Trial. *World Journal of Surgery* [Online]. 2019;43(2):580–9.
23. Law S, Fok M, Chu K, Wong J. Comparison of Hand-Sewn and Stapled Esophagogastric Anastomosis After Esophageal Resection for Cancer: A Prospective Randomized Controlled Trial. *Annals of Surgery* [Online]. 1997;226(2):169–73.
24. Liu Q, Qiu Y, Deng X, Min J, Dai J. Comparison of outcomes following end-to-end hand-sewn and mechanical oesophagogastric anastomosis after oesophagectomy for carcinoma: a prospective randomized controlled trial. *European Journal of Cardio-Thoracic Surgery* [Online]. 2015;47(3):e118–23.
25. Luechakiettisak P, Kasetsunthom S. Comparison of hand-sewn and stapled in esophagogastric anastomosis after esophageal cancer resection: a prospective randomized study. J Med Assoc Thai. 2008;91(5):681–5.
26. Mistry R, Vijayabhaskar R, Karimundackal G, Jiwnani S, Pramesh C. Effect of Short-term vs Prolonged Nasogastric Decompression on Major Postesophagectomy Complications: A Parallel-Group, Randomized Trial. Archives of Surgery [Online]. 2012;147(8):747–51.
27. Nederlof NW, Tilanus HK, Tran TJ, Hop WL, Wijnhoven B, De Jonge J. End-to-End Versus End-to-Side Esophagogastrostomy After Esophageal Cancer Resection: A Prospective Randomized Study. Annals of Surgery [Online]. 2011;254(2):226–33.
28. Okuyama M, Motoyama S, Suzuki H, Saito R, Maruyama K, Ogawa J. Hand-Sewn Cervical Anastomosis Versus Stapled Intrathoracic Anastomosis After Esophagectomy for Middle or Lower Thoracic Esophageal Cancer: A Prospective Randomized Controlled Study. Surgery Today [Online]. 2007;37(11):947–52.
29. Saluja S, Ray S, Pal S, Sanyal S, Agrawal N, Dash N, et al. Randomized Trial Comparing Side-to-Side Stapled and Hand-Sewn Esophagogastric Anastomosis in Neck. Journal of Gastrointestinal Surgery [Online]. 2012;16(7):1287–95.
30. Zhang Y, Gao B, Wang H, Su Y, Yang Y, Zhang J, et al. Comparison of Anastomotic Leakage and Stricture Formation following Layered and Stapler Oesophagogastric Anastomosis for Cancer: A Prospective Randomized Controlled Trial. Journal of International Medical Research [Online]. 2010;38(1):227–33.
31. Tabira Y, Sakaguchi T, Kuhara H, Teshima K, Tanaka M, Kawasuji M. The width of a gastric tube has no impact on outcome after esophagectomy. (Scientific papers). American Journal of Surgery [Online]. 2004;187(3):417–21.
32. Valverde A, Hay J, Fingerhut A, Elhadad A. Manual versus mechanical esophagogastric anastomosis after resection for carcinoma: A controlled trial. Surgery [Online]. 1996;120(3):476–83.
33. Rindani R, Martin CJ, Cox MR. (1999) Transhiatal versus Ivor-Lewis oesophagectomy: is there a difference? The Australian and New Zealand journal of surgery. 69 (3), 187–194. [online]. Available from: http://search.proquest.com/docview/69617458/.
34. Hulscher JB, Tijssen JG, Obertop H, van Lanschot JJ. Transthoracic versus transhiatal resection for carcinoma of the esophagus: a meta-analysis. The Annals of Thoracic Surgery. 2001;72(1):306–13.
35. Chadi S, Fingerhut A, Berho M, DeMeester S, Fleshman J, Hyman N, et al. Emerging Trends in the Etiology, Prevention, and Treatment of Gastrointestinal Anastomotic Leakage. *Journal of Gastrointestinal Surgery* [Online]. 2016;20(12):2035–51.
36. Kassis E, Kosinski A, Ross P, Koppes K, Donahue J, Daniel V. Predictors of Anastomotic Leak After Esophagectomy: An Analysis of The Society of Thoracic Surgeons General Thoracic Database. *The Annals of Thoracic Surgery*. [Online]. 2013;96(6):1919–26.
37. Moher D, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Annals of internal medicine. 2009;151(4):264–9. https://doi.org/10.7326/0003-4819-151-4-200908180-00135.

Tables

Table 1. Characteristics of the Included Studies and Participants Studies

First author (year)	Country	Total participants (N)	Total participants in intervention groups (n)	Prevalence AL (%)	Male-to-female ratio evaluated (T, I, C)	Age, years (y) Mean ± SD	Neoadjuvant therapy	Follow-up, months (mo, wk, or y) Mean ± SD
Bhat 2006[6]	India	194	97	8.8	T: 3:1.8	T: 52.5	Excluded patients with previous neoadjuvant Tx	F/U every 3-mo for 3 y post-op every 4- to 6-mo post-op
Dai 2011[5]	China	253	127	3.1	T: 4:01	T: 63.5	Excluded patients with previous neoadjuvant Tx	*22 mo (3-52 mo)
Daryaei 2008[19]	Iran	40	18	15	NR	T: 58.4 ± 10.3	NP	NP
Gupta 2001[20]	India	100	48	12	I: 0.8:1 C: 0.7:1	I: 51.3 ± 13.0 C: 50.8 ± 13.2	Rad **±** Chemo: 22/100 and Chemo alone: 56/100	3 mo or more
Hayashi 2019[21]	Japan	71	34	5.6	T: 6:8	T: 63.04	NP	NP
Law 1997[22]	Hong Kong	122	61	3.3	I: 7.7:1 C: 6.6:1	I: 64 ± 1.2 C: 63 ± 1.0	NP	20 (SD 2.2) mo hand-sewn and 19 (2.2) mo stapled group (p= NS)
Liu 2014[7]	China	378	188	4.2	T: 3:01	T: 64	Excluded patients with previous neoadjuvant Tx	NP
Liu 2015[23]	China	432	219	5	I: 3:1 C: 3:1	I: 62 ± 8 C: 61 ± 9	Rad + chemo: 64/478	17.8 (3.2) mo hand-sewn and 18.3 (3.4) mo stapled
Luechakiettisak 2008[24]	Thailand	104	52	4.8	I: 4.8:1 C: 5.6:1	I: 63.6 C: 62.0	NP	NP
Mistry 2012[25]	India	253	127	3.1	T: 2.1:1	I: 53.4 C: 56.7	Rad **±** Chemo: 2/150 and Chemo alone: 72/150	NP
Nederlof 2011[26]	Netherlands	128	64	31	I: 2:1 C: 7:1	I: 60 C: 63	Rad + Chemo: 27/64 and Chemo alone: 17/64	3- or 6-wk outpatient visit. 3 mo first y post-op. Every 4 mo second y post-op.
Okuyama 2007[27]	Japan	32	14	12	I: 13:1 C: 16:2	I: 63.6 C: 64.3	Excluded patients with previous neoadjuvant Tx	5 y

First author (year)	Country	Total participants (N)	Total participants in intervention groups (n)	Prevalence AL (%)	Male-to-female ratio evaluated (T, I, C)	Age, years (y) Mean ± SD	Neoadjuvant therapy	Follow-up, months (mo, wk, or y) Mean ± SD
Saluja 2012[28]	India	174	87	17	I: 2.3:1 C: 1.6:1	I: 51.4 ± 12 C:50.9 ± 14	Rad + Chemo: 107/174	NP
Zhang 2010[29]	China	516	272	1.4	I: 1.4:1 C: 1.4:1	I: 59 ± 1.2 C: 60 ± 1.3	Excluded patients with previous neoadjuvant Tx	12 mo
Zheng 2013[4]	China	164	82	8.5	I: 1.6:1 C: 1.4:1	I: 67.5 ± 11.2 C: 65.7 ± 9.4	None of the patients received chemotherapy or radiotherapy pre-op	3 y
Tabira 2004[30]	Japan	44	22	14	I: 6.3:1 C: 10:1	I: 64 ± 8 C: 60 ± 8	NP	NP
Valverde 1996[31]	France	152	78	16	I: 9.6:1 C: 10.1:1	I: 59 ± 9 C: 59 ± 10	NP	NP

Abbreviations: C, control; Chemo, chemotherapy; I, intervention; mo, months; NP, not provided; pre-op, pre-operatively; post-op, post-operatively; Rad, radiation; SD, standard deviation; Tx, therapy; wk, weeks; Y, years
*Median (range)

Table 2. Intervention Characteristics of the Included Studies

First author (year)	Intervention and control groups	Surgical approach to intervention	Length of Stay, days	Diagnostic modality for anastomosis	Medical management	Endoscopic management	Surgical management
Bhat 2006[6]	Omentoplasty (I) vs hand-sewn anastomosis alone (C)	Cervical: 102 Thoracic: 92	NP	Water-soluble contrast	Abx, bronchodilators, chest physiotherapy	Re-insertion NG tube	Re-exploration, refashioning anastomosis
Dai 2011[5]	Omentoplasty (I) vs stapled anastomosis alone (C)	Cervical: 75 Thoracic: 180	I: 20.4 (11.5)** C: 23.1 (15.2)**	Contrast	NP	NP	NP
Daryaei 2008[19]	NG tube (I) vs Metoclopramide (C)	Cervical: 20 Thoracic: 20	I: 10.9 (3.5)** C: 13.9 (8.2)**	Gastrografin contrast	Metoclopramide (C)	NP	NP
Gupta 2001[V20]	Subtotal (I) vs slender anastomosis (C)	Cervical only	I: 10.7 (3.6)** C: 11.9 (5.6)**	Water-soluble contrast	Not reported	NP	NP
Hayashi 2019[V21]	No or early NG tube removal (I) vs prolonged NG tube (C)	Thoracic only	I: 25.7 (12.76)** C: 29.4 (18.06)**	Contrast agent	All patients received PPI, ICU admission post-op	Re-insertion of NG tube	Tracheostomy, mini-tracheostomy
Law 1997[22]	Stapler (I) vs hand sewn anastomosis (C)	Thoracic only	NP	Gastrografin contrast, endoscopy	NP	NP	NP
Liu 2014[7]	Valvuloplasty (I) vs stapled anastomosis alone (C)	Cervical: 126 Thoracic: 259	I: 20.4 (11.5)** C: 22.1 (15.2)**	Contrast, endoscopy	NP	NP	NP
Liu 2015[23]	Stapler (I) vs hand sewn anastomosis (C)	Cervical: 113 Thoracic: 354	I: 20.1 (6.8)** C: 18.9 (7.3)**	Barium swallow, endoscopy	Nutrition, chest tube drain	NP	NP
Luechakiettisak 2008[24]	Stapler (I) vs hand sewn anastomosis (C)	Thoracic only	NP	Gastrografin contrast	NP	NP	NP
Mistry 2012[25]	Short-term (I) vs prolonged NG tube (C)	Cervical: 33 Thoracic: 117	I: 12 (9 – 17)* C: 12 (10 – 17)*	Contrast	NP	NP	NP
Nederlof 2011[V26]	End-to-end (I) vs side-to-end (C) anastomosis	Cervical: 88 Thoracic: 40	I: 15 (9 – 125)* C: 22 (8 – 281)*	Contrast, endoscopy, neck wound saliva	NP	NP	Re-operation

First author (year)	Intervention and control groups	Surgical approach to intervention	Length of Stay, days	Diagnostic modality for anastomosis	Medical management	Endoscopic management	Surgical management
Okuyama 2007[27]	Stapler (I) vs hand sewn anastomosis (C)	Cervical: 18 Thoracic: 14	NP	Water-soluble contrast	Conservative	NP	NP
Saluja 2012[28]	Stapler (I) vs hand sewn anastomosis (C)	Cervical only	I: 12.8 (8)** C: 11.9 (6)**	Gastrografin contrast	Abx, opening neck wound	NP	NP
Zhang 2010[29]	Stapler (I) vs hand sewn anastomosis (C)	Thoracic only	NP	Chest tube output, contrast barium, endoscopy	Nutrition, chest tube drain	NP	NP
Zheng 2013[4]	Omentoplasty (I) vs hand-sewn anastomosis (C)	Thoracic only	I: 21 (5)** C: 23 (6)**	Gastrografin contrast	NP	NP	NP
Tabira 2004[30]	Subtotal (I) vs slender gastric tube (C)	Thoracic only	NP	NP	Conservative	NP	NP
Valverde 1996[V31]	Stapler (I) vs hand sewn anastomosis (C)	Cervical: 45 Thoracic: 107	NP	Swallow, methylene blue, interstitial fluid in drains	NP	NP	NP

Abbreviations: Abx, antibiotics; C, control; I, intervention; mo, months; NP, not provided; POD, post-operative day; TE, transesophageal; TH, transhiatal; TT, transthoracic; wk, weeks; Y, years

*Median (IQR)

**Mean (SD)

[V]Excluded from meta-analysis (Valverde 1996, Group results influenced by multiple additional interventions; Nederlof 2011, only study to report intervention type; Hayashi 2019, excluded from AL pooled results because of restriction to reporting grade 3+ AL only; Gupta 2001, only study to report intervention type)

Table 3. Risk ratios for anastomotic leak for omentoplasty intervention (sub-group by cervical or thoracic approach)

Group	Study (Author, year)	Risk ratio	95% CI (lower, upper)	I^2
Cervical*	Bhat 2006[6]	0.22	0.080, 0.88	-
Dai 2011[5]	0.26	0.030, 2.08	-	
Overall (n = 2 studies)	0.23	0.080, 0.88	0	
Thoracic*	Bhat 2006[6]	0.19	0.020, 1.52	-
Dai 2011[5]	0.18	0.010, 3.68	-	
Overall (n = 2 studies)	0.19	0.030, 1.03	0	

**omentoplasty vs. stapled or hand-sewn anastomosis*

Table 4. Summary of Findings (11 meta-analyzed studies)

Intervention	No. Participants (studies)	Quality of Evidence	Measure of effect, RR (95% CI)
Omentoplasty vs conventional anastomosis[ℓ]	611 (3 studies)	**+ + + + (high quality)** -1: unclear risk of bias[1] +1: large magnitude of effect	RR = 0.22 (78% risk reduction) 95% CI = 0.1, 0.5[*]
Early or no NG tube decompression vs standard	374 (2 studies)	+ + + - (**moderate quality**) -2: high risk of bias[2] +1: large magnitude of effect	RR = 0.38 (62% risk reduction) 95% CI = 0.04, 3.51
Stapled vs hand-sewn anastomosis	1532 (6 studies)	- - - - (**very low quality**) -2: high risk of bias[2] -1: imprecision in measure of effect[3] -1: inconsistency across studies[4]	RR = 0.92 (8% risk reduction) 95% CI = 0.45, 1.87

RR: Risk ratio; **CI:** Confidence Interval

GRADE: working group grades of evidence

High quality (+ + + +): more research very unlikely to change the estimate of effect

Moderate quality (+ + + -): means further research is likely to have an important impact on our confidence in the estimate of effect and may alter the estimate

Low quality (+ + - -): means that the effect estimate is limited and may substantially differ from

Very low quality (+ - - - or **- - - -):** grade means that we have little confidence in the effect estimate

[*]statistically significant confidence interval

[ℓ]stapled or hand-sewn anastomosis

[1]one study lacked allocation concealment

[2]lack of randomization and allocation concealment

[3]optimal information size not met (**appendix 8**) and the 95% CI for the effect estimate crosses the null (RR = 1.0)

[4]moderate heterogeneity (I^2 = 40.1%)

Figures

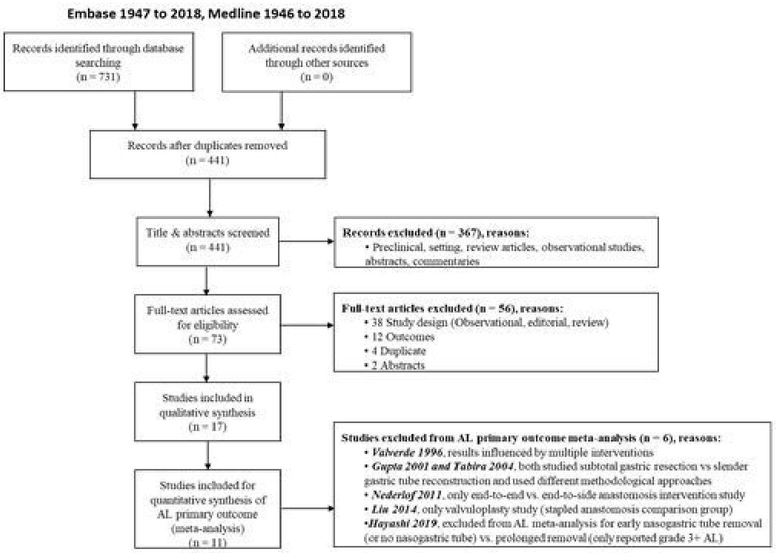

Figure 1

PRISMA flow diagram summarizing screening and selection of eligible studies.

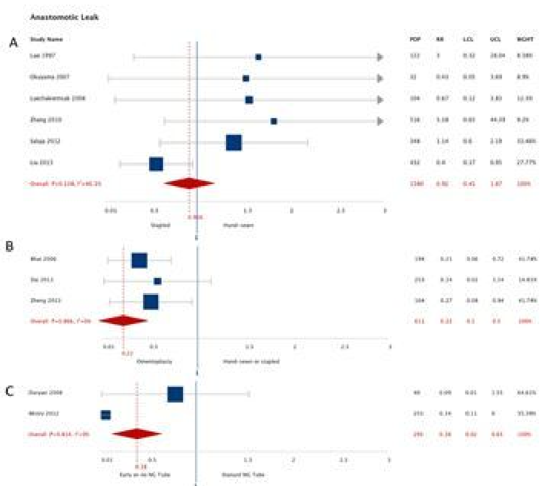

Figure 2

Pooled risk ratio for anastomotic leakage according to intervention type (11 meta-analyzed studies). Stapled anastomosis intervention compared to hand-sewn (Panel A). Omentoplasty intervention compared to hand-sewn or stapled anastomosis (Panel B). Early removal or no nasogastric tube intervention compared to prolonged nasogastric tube removal (Panel C).

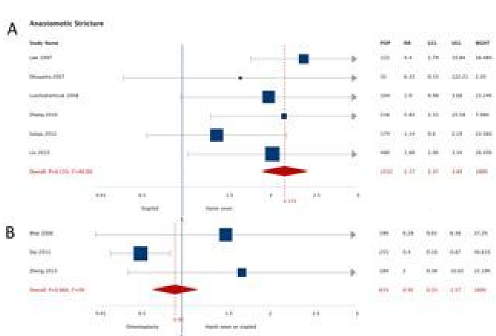

Figure 3

Pooled risk ratio for anastomotic stricture grouped according to intervention type (11 meta-analyzed studies). Stapled anastomosis intervention compared to hand-sewn (Panel A). Omentoplasty intervention compared to hand-sewn or stapled anastomosis (Panel B).

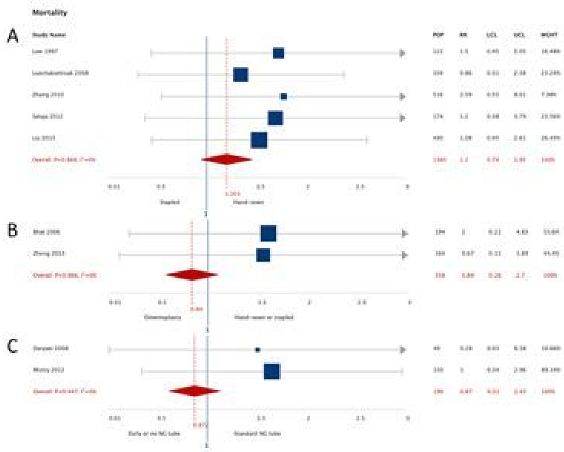

Figure 4

Pooled risk ratio for mortality grouped according to intervention type (11 meta-analyzed studies). Anastomotic stricture grouped by intervention type. Stapled anastomosis intervention compared to hand-sewn (Panel A). Omentoplasty intervention compared to hand-sewn or stapled anastomosis (Panel B). Early removal or no nasogastric tube intervention compared to prolonged nasogastric tube removal (Panel C). Overall mortality reported across studies except when marked (*) as 30-day mortality.

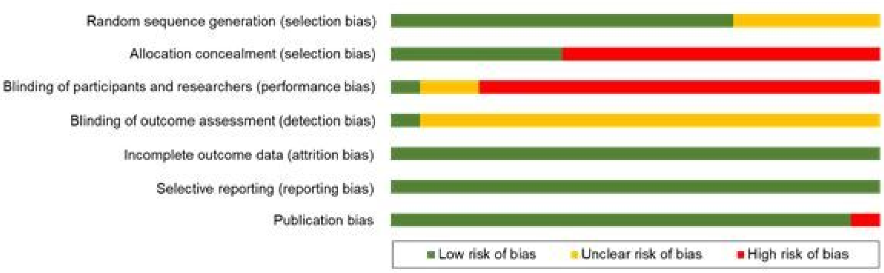

Figure 5

Revised Cochrane risk of bias tool for randomized controlled trial studies included (11 meta-analyzed studies). Green, low risk of bias; yellow, unclear risk of bias; and red, high risk of bias.

Supplementary Files

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- SupplementalfilesDDS.docx