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Comparison of the safety and efficacy between linear stapler and circular stapler in totally laparoscopic total gastrectomy: protocol for a systematic review and meta-analysis

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Comparison of the safety and efficacy between linear stapler and circular stapler in totally laparoscopic total gastrectomy: protocol for a systematic review and meta-analysis

Running Head: Protocol for a meta-analysis of linear versus circular stapler in TLTG

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Abstract

Introduction: Total gastrectomy is often required for upper body gastric cancer, and totally laparoscopic total gastrectomy (TLTG) is deemed to be a promising choice of operation because of its all the well-known advantages such as less invasion and quick postoperation recovery. However, the anastomosis between esophagus and jejunum is the difficulty of TLTG. Although staplers have promoted the development of TLTG, the choice of the stapler to complete esophagojejunostomy is controversial and unclear, because both the linear and circular staplers have their advantages and disadvantages. Therefore, a higher level of research evidence is needed to compare the safety and efficacy between the two types of staplers for esophagojejunostomy in TLTG for gastric cancer.

Methods and analysis: PubMed, Embase, Cochrane Library, CNKI and Wanfang Databases will be comprehensively searched. All eligible RCTs, non-RCTs, or observational studies comparing the two types of staplers will be included. Meta-analysis will be then performed using Review Manager 5.3 software to compare the safety and efficacy between linear and circular staplers for esophagojejunostomy in TLTG. The primary outcomes are anastomotic leakage, anastomotic stricture, anastomotic haemorrhage, etc. The secondary outcomes include first exhaust time after operation, first feeding time, total operation time, reconstruction time, estimated blood loss, etc. The heterogeneity of this study will be assessed by P values and I^2 statistic. Subgroup analyses and sensitivity analyses will be used to explore and explain the heterogeneity. The risk of bias will be assessed using the Cochrane tool or the Newcastle-Ottawa Quality Assessment Scale. Publication bias will be investigated through funnel plots drawn using the STATA SE 12.0 software.

Ethics and dissemination: Ethical approval will not be required because this proposed systematic review and meta-analysis is based on previously published data, which do not include data on

interventions on patients.

PROSPERO registration number: CRD42018111680.

Keywords: linear stapler; circular stapler; totally laparoscopic total gastrectomy; esophagojejunostomy

Strengths and limitations of this study

(1) To our best knowledge, this review will be the first systematic review and meta-analysis to compare the safety and efficacy of the linear stapler and circular staplers in TLTG.

(2) The study selection, data extraction, and quality assessment of the studies will be performed by three independent reviewers.

(3) Subgroup analyses and sensitivity analyses will be used to explore and explain the heterogeneity.

(4) Some observational studies might be included in this study, and might affect the quality of the evidence.

(5) There might be some selection bias in this systematic review and meta-analysis, because the retrieved databases are limited to English and Chinese database.

1 Introduction

Gastric cancer is a common malignant tumor of the digestive tract, and its morbidity and mortality rank 5th and 3rd among global malignant tumors, respectively.[1] Due to improved surveillance, the overall incidences of worldwide gastric cancer has been decreased, but the incidences of upper body gastric cancer have been increasing.[2 3] Radical resection is still the only curative modality for primary treatment of patients with resectable gastric cancer, and total gastrectomy is often required for upper body gastric cancer.[3 4] Laparoscopic technique is the main development direction of surgical treatment for gastric cancer. The results of a multi-center retrospective cohort study have shown that laparoscopic total gastrectomy (LTG) could achieve comparable oncological outcomes to open total gastrectomy (OTG).[5] Furthermore, with the development of laparoscopic equipment and the accumulation of laparoscopic techniques experience, the laparoscopic surgery in gastric cancer has experienced a transition from laparoscopic-assisted surgery to totally laparoscopic surgery with less invasion and quick postoperative recovery.[6]

However, the anastomosis and reconstruction of esophagojejunostomy is the focal point and difficulty of totally laparoscopic total gastrectomy (TLTG).[6] Presently, the two commonly used anastomosis methods for esophagojejunostomy are circular stapler anastomosis and linear stapler anastomosis.[6-8] In consideration of the characteristics of laparoscopic surgery, the traditional circular anastomosis has certain limitations. For example, the circular stapler cannot be placed through a trocar, and it needs to be placed in the abdominal cavity through a small assisted incision in the abdomen, thereby reducing the benefit of laparoscopic surgery. Although OrVil™ does not pass through the abdominal cavity, the top-down placement method is required, but the operation requires

an anesthesiologist to cooperate.[9] Compared with the circular stapler, the esophagojejunostomy using linear stapler has some advantages.[10] For example, it is easy to enter the abdominal cavity through the trocar, without purse-string suture, and the instrument used is easier to operate. The primary disadvantage of linear anastomosis is the need to retain a long enough length of esophageal stump for the anastomosis, which limits the surgical margin and could increase the tension of the anastomosis. For this reason, some academics consider that it is not appropriate for patients with tumors located in the upper stomach or close to the esophago-gastric junction or tumors with esophageal invasion.[11 12]

Therefore, the choice of the staplers to use for complete esophagojejunostomy of TLTG is still an unclear and controversial topic.[7 8 13] Previous reports on contrasting linear and circular stapling anastomosis for esophagojejunostomy in TLTG mostly are retrospective and are based on small-sample studies, further, there exists some contradictory results in the different studies. Therefore, the safety and efficacy of linear stapling anastomosis has not been well resolved in these studies and remains to be confirmed by higher-level evidence. In view of this, a systematic review and meta-analysis will be conducted based on relevant published literature to further explore and compare the safety and efficacy of the linear stapler and circular stapler in TLTG, with the hope of providing a reference to help surgeons choose a better stapler.

2 Materials and methods

The protocol of the planned systematic review and meta-analysis was prepared in accordance with the recommendation from the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement,[14] and this systematic review and meta-analysis will be written in line with PRISMA statement.[15] In addition, this study protocol was registered with the

international prospective register of systematic reviews PROSPERO (CRD42018111680).[16]

2.1 Literature-search strategy

PubMed, Cochrane Library, Embase, CNKI, Wanfang Database search will be comprehensively carried out for all relevant studies in accordance with the population, intervention, control and outcomes (PICO) criteria between Jan-1990 and actual start date. The studies comparing linear stapler with circular stapler for esophagojejunostomy in TLTG will be considered. The following MeSH terms and their combinations will be searched in [Title/Abstract]: i) "*linear stapler*" OR "*overlap*" OR "*FEEA*" OR "*T-shaped*" OR "*π-shaped*" OR "*delta-shaped*"; ii) "*circular stapler*" OR "*OrVil™*" OR "*hemidouble stapling technique*" OR "*double stapling technique*"; iii) "*totally laparoscopic*"; iiii) "*total gastrectomy*". The related-articles function is used to broaden the search, and the computer search is supplemented with manual searches of the reference lists of all retrieved studies, review articles and conference abstracts.

2.2 Inclusion criteria

(1) The subjects were the patients who had undergone esophagojejunostomy in totally laparoscopic total gastrectomy, and preoperative or postoperative histopathologic examination confirmed gastric cancer; (2) According to the different anastomosis methods used for esophagojejunostomy in digestive tract reconstruction, patients were divided into linear stapling anastomosis and circular stapling anastomosis groups; (3) The study types were randomized controlled trials (RCTs), non-RCTs, or observational comparative studies; (4) The original literature had the terms including intraoperative conditions, postoperative specimens, postoperative recovery, postoperative complications, postoperative complications, or had at least one research data; (6) Pooled results can be formulated by the statistical index, such as odds ratio (OR), relative risk (RR),

or weighted mean difference (WMD). (6) For multiple documents from the same research institution, a recent or higher quality research will be selected.

2.3 Exclusion criteria

(1) The literature included cases of open surgery or hand-assisted laparoscopic total gastrectomy; (2) The literature that did not respectively provide the data for linear stapler group and circular stapler group or the surgical method was not clearly stated in the literature; (3) The literature was a case report, case series, letters, review, or non-control study without control group; (4) The sample size was too small, and the number of cases was less than 20 cases; (5) Other treatments were differently performed between two groups during pre and post operation, and these treatments probably affected the observed outcome of the studies; (6) The literature was a repeated publication.

2.4 Study screening and selection

Any duplication will be found and removed using EndNote X8 reference management software (Clarivate Analytics, Thomson Place, Boston, USA). Under the pre-established inclusion and exclusion criteria, the titles and abstracts of all remaining literatures are carefully read and examined to exclude obviously unrelated documents. The full text of screened literature will be then deeply and carefully read to determine whether it is to be included. All steps will be independently conducted and cross-checked by three reviewers, and all disagreements are resolved by discussion with the senior authors (Xueqing Yao) until a consensus be reached. The detailed process of study selection will be recorded in detail in a PRISMA-compliant flow diagram (Figure 1).

2.5 Data extraction and outcomes of interest

Three reviewers will independently extract the data, and any discrepancy will be resolved by discussion until a consensus reached. All extracted data will be filled in data extraction sheets created

by Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington, USA). The main extracted information are as follows: (1) study characteristics (e.g: first author's name, year of publication, country of study, study design, study period, number of patients, number of patients with linear stapler, number of patients with circular stapler, etc); (2) participant characteristics (e.g: age, sex, ethnicity, body mass index (BMI), cancer stage, American Society of Anesthesiologists (ASA) score etc); (3) primary outcomes: anastomotic leakage, anastomotic stricture, anastomotic haemorrhage, total postoperative complications; (4) secondary outcomes: first exhaust time after operation, first feeding time, total operation time, reconstruction time of digestive tract, estimated blood loss, lymph node harvest, the distance from the proximal margin of the tumor, postoperative hospital stay. Any missing information is supplemented by contacting the original author by telephone or e-mail.

2.6 Quality assessment

Study quality will be independently scored by three reviewers using the Cochrane risk of bias tool or the Newcastle-Ottawa Quality Assessment Scale (NOS).[17] The methodological quality of randomized controlled trials will be assessed by the Cochrane risk of bias tool.[18] The methodological quality of nonrandom studies as case-control and cohort studies will be assessed by the NOS, which consists of three factors: patient selection, comparability of the study groups, and assessment of outcome. A score of 0–9 (allocated as stars) be allocated to each study except for RCTs. RCTs and observational studies achieving six or more stars be considered to be of high-quality studies. In cases where discrepancies arose, studies will be re-examined and a consensus will be reached through discussion.

2.7 Statistical analysis

All the meta-analyses will be performed using Review Manager 5.3 (Cochrane Collaboration,

Oxford, UK). The weighted mean difference (WMD) and odds ratio (OR) be used to compare continuous and dichotomous variables respectively, and all the results will be reported with 95% confidence intervals. For the literature reporting median and range of continuous variables, the mean and standard deviation (SD) will be extracted using the method described by Hozo et al.[19] Continuous variables that only provided quartiles or whose mean and SD could not be extracted will be eliminated. Assessment of statistical heterogeneity between the studies will be undertaken using the $\chi 2$ and I^2 statistical tests. There is no obvious statistical heterogeneity between the studies when P value ≥ 0.1 or $I^2 \leq 50\%$, and the fixed effect model will be used for meta-analysis. Conversely, there is statistical heterogeneity between the studies when P value < 0.1 or $I^2 > 50\%$, and a random effect model will be used for meta-analysis. If concerns for high heterogeneity (I^2 value >75% indicates high heterogeneity)[20] exist, a sensitivity analysis will be performed.

2.8 Assessment of publication bias

The potential publication bias will be investigated using funnel plots drawn by the STATA SE version 12.0 software. The publication bias will be assessed by visual inspection of the Begg's funnel plots, whereby, if the standard error of logOR of each study is plotted against its logOR, an asymmetric plot suggests a possible publication bias.[21] In addition, we will also perform the Egger linear regression test at the $p<0.10$ significance level to assess the funnel-plot's asymmetry.[22]

2.9 Subgroups analysis

To explore the potential heterogeneity, subgroup meta-analyses will be performed based on different characteristics of the patient (e.g: age, sex, ethnicity, BMI, cancer stage, etc) as well as by study characteristics (e.g: country of study, study design, year of publication, study period, number of patients, etc).

2.10 Sensitivity analysis

In order to ensure the robustness and reliability of evidence, sensitivity analysis will be performed to assess the effect of studies with a high risk of bias. The results will be compared to decide whether low-quality studies should be excluded based on sample size and quality assessment of studies or effect on pooled effective size. In addition, a leave-one-out sensitivity meta-analysis might be considered if a study involved a large number of patients was based on different types of studies.[23]

3 Discussion

With the accumulation of laparoscopic experience and the development of laparoscopic equipment, laparoscopic surgery for gastric cancer has greatly developed in recent decades. Not only the application range of laparoscopic surgery for gastric cancer has been expanded,[24 25] but the laparoscopic reconstruction of the digestive tract in gastric cancer has experienced a transition from laparoscopic-assisted surgery to totally laparoscopic surgery.[6] However, the technique of total laparoscopic digestive tract reconstruction is the difficulty of TLTG, which has not been widely carried out around the world due to its high technical requirements for surgeons.[13 26] However, total laparoscopic digestive tract reconstruction after TLTG has obvious theoretical advantages,[27 28] such as pneumoperitoneum providing a larger operation space for surgery and multi-angle lens providing direct vision for operation to avoid damage. Therefore, TLTG is a promising technique for gastric cancer.

It is no doubt that, the development of stapler has promoted the development of laparoscopic gastrointestinal operation, especially in TLTG. Presently, mechanical anastomosis for

esophagojejunostomy in TLTG is mainly divided into two types: end-to-side anastomosis using the circular stapler and side-to-side/ functional end-to-end anastomosis using the linear stapler. [6-8]

The circular stapling anastomosis method is divided into different methods according to the placement of the nail anvil: the traditional method of direct insertion, reverse anvil method and OrVil™ method.[29-31] However, in the first two methods, the main body of the stapler cannot enter the abdominal cavity through the trocar, the pneumoperitoneum must be closed and a small auxiliary incision is often needed, thereby reducing the fluency of the operation. In addition, the difficult in operation of the esophageal purse suture and the placement of the nail anvil also limits the application of these two methods. While the OrVil™ method does not require the placement of an anvil through the abdominal cavity, which has certain disadvantages that the OrVil™ method requires the cooperation of an anesthesiologist and requires a special anvil placement device.[9] The price of the special device is high, and the extraction of the guide tube might cause intra-abdominal infection.[9 26 32]

Linear stapling anastomosis involves functional end-to-end anastomosis (FEEA method) as well as side-to-side anastomosis (Overlap method) [33] and has absolute advantage in total laparoscopic gastrectomy compared with the disadvantages of circular stapling anastomosis.[11 28 32] Based on the published literatures and the experience of our center, the advantages of linear stapler are mainly reflected in that[27 34 35]: (1) linear stapler can be more easily accessed into the abdominal cavity via trocar and has a better visual field; (2) the operation of linear stapler is simple and convenient, and the requirement for the surgeon is lower than that of using a circular stapler; (3) composed with the circular stapler with two rows of staples, the line stapler can use three rows of nail technology to theoretically improve the safety of the anastomosis. However, although some advantages have been

reported for linear stapler, its application in laparoscopic total gastrectomy has some limitations such as [8 13]: (1) retaining a longer stump of the esophagus is required which lead to limited incisal margin; (2) when the anastomosis plane is higher than the plane of esophageal hiatus, the operation is performed in a narrow thoracic cavity and the visual field is easily restricted; (3) the pulling and folding of the jejunum arm might increase the tension of the anastomosis. Whether the possibly increased tension could increase the risk of anastomotic leak is an important topic needed to be resolved in this study. The discussed anastomotic methods have their advantages and disadvantages in the anastomosis of the esophagus between jejunum, and it is not clear which anastomosis technique is superior.[13] Further, no standard methods have been established to guide the selection.[36 37] Therefore, it is meaningful and necessary to conduct a systematic review and meta-analysis to provide a reference that could aid clinical surgeons in choosing a more appropriate alternative for their patients.

In this review, in order to collect all existing and available literature, RCTs and non-RCTs as well as observational studies will be included. Because of the novelty of this research topic, a few studies had been reported. However, the non-RCTs and observational studies might affect the quality of the evidence and lower the confidence level of the result. Besides, there are many influencing factors such as different standards in choosing patients, different proficiency in laparoscopic techniques and different habits or methods of using the stapler by different surgeons in different regions, which might have impacted the results. Hence, in view of these, it is very important for this review to perform subgroup analysis and sensitivity analysis. Further analysis and explanations will be carried out in our studies to ensure the robustness and reliability of the results.

In summary, this systematic review and meta-analysis will help to determine the difference in

terms of safety and efficacy between linear stapler and circular stapler in TLTG. Furthermore, the findings of this study will not only help the surgeons in chosing the surgical methods, but also might benefit more patients in the future.

Abbreviations

LTG: laparoscopic total gastrectomy; TLTG: totally laparoscopic total gastrectomy; OTG: open total gastrectomy; PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols; RCTs: randomized controlled trials; CNKI: China national knowledge infrastructure; ASA: American Society of Anesthesiologists; NOS: Newcastle-Ottawa Quality Assessment Scale; BMI: body mass index; FEEA: functional end-to-end anastomosis; WMD: weighted mean difference; SD: standard deviation; CI: confidence intervals.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Wrote the paper: Tianyou Liao, Leilei Deng. Study concept and design: Manzhao Ouyang, Xueqing Yao. Registered the protocol in the PROSPERO database: Tianyou Liao, Manzhao Ouyang. Preliminary literature search: Tianyou Liao, Leilei Deng. Corrected and revised manuscript: Manzhao Ouyang, Xueqing Yao. Approving current version of manuscript: Tianyou Liao, Leilei Deng, Xueqing Yao, Manzhao Ouyang.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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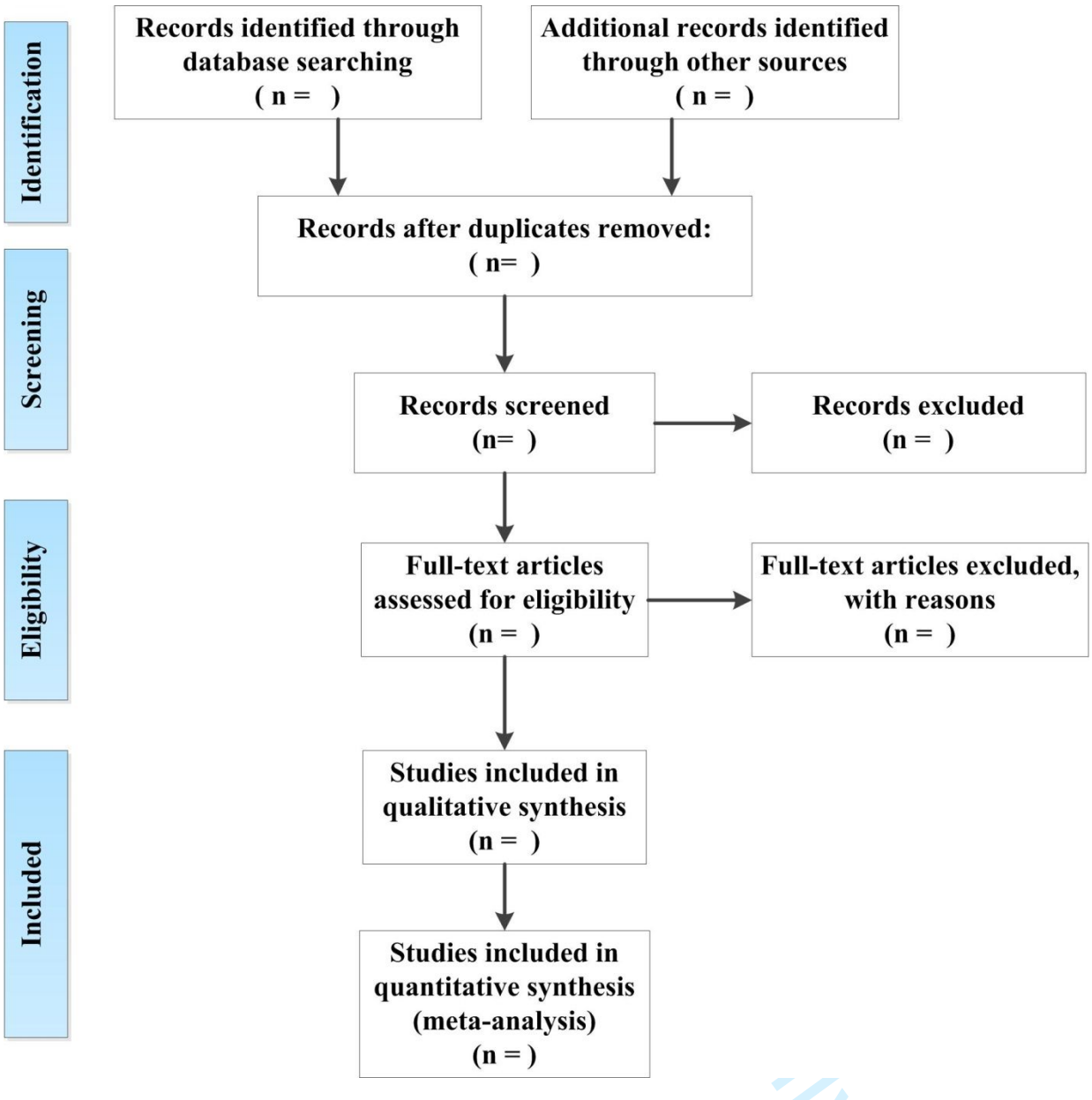
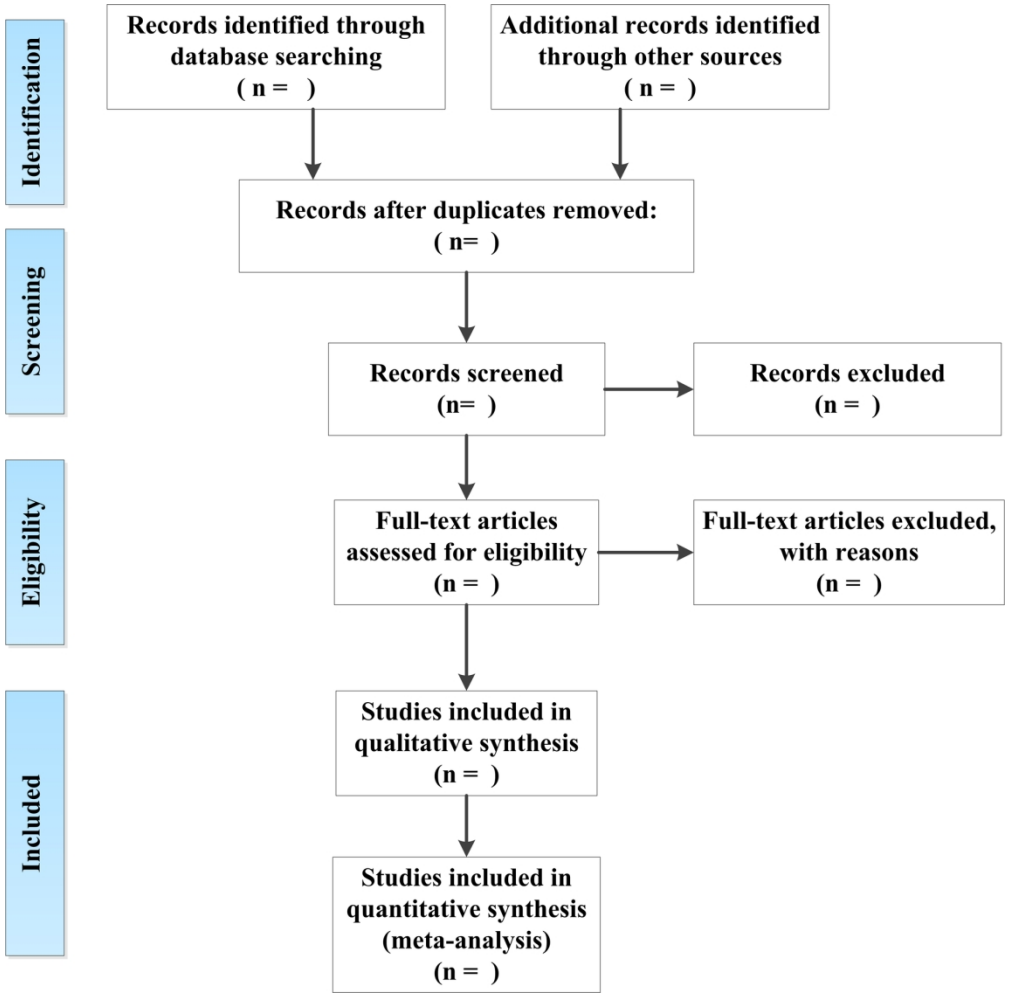
Figure 1 Flow diagram of study selection





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Running Head: Protocol for a meta-analysis of linear versus circular stapler in TLTG

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Abstract

Introduction: Total gastrectomy is often recommended for upper body gastric cancer, and totally laparoscopic total gastrectomy (TLTG) is deemed to be a promising choice of operation because of its all the well-known advantages such as less invasion and quickly postoperative recovery. However, the anastomosis between esophagus and jejunum is the difficulty of TLTG. Although staplers have promoted the development of TLTG, the choice of suitable staplers to complete esophagojejunostomy is controversial and unclear, because both linear and circular staplers have their advantages and disadvantages. Therefore, a higher level of research evidence is needed to compare the two types of staplers in terms of safety and efficacy for esophagojejunostomy in TLTG among patients with gastric cancer.

Methods and analysis: PubMed, Embase, Cochrane Library, CNKI and Wanfang Databases will be comprehensively searched. All eligible RCTs, non-RCTs, or observational studies comparing the two types of staplers will be included. A meta-analysis will be performed using Review Manager 5.3 software to compare the safety and efficacy of linear and circular staplers for esophagojejunostomy in TLTG. The primary outcomes are anastomotic leakage, anastomotic stricture, anastomotic hemorrhage. The secondary outcomes include first exhaust time after operation, first feeding time, total operation time, reconstruction time, estimated blood loss. The heterogeneity of this study will be assessed by P values and I^2 statistic. Subgroup analyses and sensitivity analyses will be used to explore and explain the heterogeneity. The risk of bias will be assessed using the Cochrane tool or the Newcastle-Ottawa Quality Assessment Scale. Publication bias will be investigated through funnel plots drawn using the STATA SE 12.0 software.

Ethics and dissemination: Ethical approval will not be required because this proposed systematic review and meta-analysis is based on previously published data, which does not include intervention data on patients.

PROSPERO registration number: CRD42018111680.

Keywords: linear stapler; circular stapler; totally laparoscopic total gastrectomy; esophagojejunostomy

Strengths and limitations of this study

(1) To our best knowledge, this review will be the first systematic review and meta-analysis to compare the safety and efficacy of the linear stapler and circular staplers in TLTG.

(2) The study selection, data extraction, and quality assessment of the studies will be performed by three independent reviewers.

(3) Subgroup analyses and sensitivity analyses will be used to explore and explain the heterogeneity.

(4) Some observational studies might be included in this study, which might affect the quality of the data.

(5) There might be some selection bias in this systematic review and meta-analysis, because the resource databases are limited to English and Chinese language.

1 Introduction

Gastric cancer is a common malignant tumor of the digestive tract, and its morbidity and mortality ranked 5th and 3rd respectively among the global malignant tumors.[1] Although the overall incidence of gastric cancer has been decreasing worldwide, the incidence of upper body gastric cancer has been on an increasing trend.[2] [3] Radical resection is the only curative modality recommended for primary treatment of patients with resectable gastric cancer, and total gastrectomy is often performed for upper body gastric cancer.[3] [4] Laparoscopic technique is one of the main development direction of surgical treatment for gastric cancer. The results of a multi-center retrospective cohort study have shown that laparoscopic total gastrectomy (LTG) could achieve comparable oncological outcomes to open total gastrectomy (OTG).[5] Furthermore, with the development of new laparoscopic equipments and the accumulation of advanced experience in the application of laparoscopic techniques, laparoscopic surgery for gastric cancer has undergone a technological transition from laparoscopic-assisted surgery to totally laparoscopic surgery which is less invasive and expedites postoperative recovery.[6]

However, the anastomosis and reconstruction of esophagojejunostomy is the focal point and difficulty of totally laparoscopic total gastrectomy (TLTG).[6] Presently, the two commonly used anastomosis methods for esophagojejunostomy are circular stapler anastomosis and linear stapler anastomosis.[6-8] Considering the characteristics of laparoscopic surgery, traditional circular anastomosis has certain inherent limitations. For example, the circular stapler cannot be placed through a trocar, and it needs to be placed in the abdominal cavity through a small assisted incision in the abdomen, thereby reducing the benefit of laparoscopic surgery. Although OrVil™ does not pass through the abdominal cavity, a top-down placement method is required, but the operation

requires an anesthesiologist to cooperate.[9] Compared with the circular stapler, linear stapler has some advantages in esophagojejunostomy.[10] For example, it can easily enter the abdominal cavity through the trocar, without purse-string suture, and the used instrument is easy to operate. The primary disadvantage of linear anastomosis is the need for a long-enough esophageal stump for anastomosis, which limits the surgical margin and could increase the tension of the anastomosis. For this reason, some scholars consider that linear anastomosis is not appropriate for patients with tumors located in the upper stomach or close to the esophago-gastric junction or tumors with esophageal invasion.[11 12] A meta-analyses comparing linear anastomosis with circular anastomosis in laparoscopic distal gastrectomy (LDG) suggested that linear anastomosis is better than circular anastomosis in LDG[13]. However, considering the differences between TLTG and LDG in terms of surgical methods, surgical objects and surgical difficulties, this conclusion cannot be applied to guide the implementation of TLTG.

Therefore, the choice of staplers for complete esophagojejunostomy of TLTG is still an unclear and controversial topic.[7 8 14] Majority of the previous comparisons on contrasting linear and circular stapling anastomosis for esophagojejunostomy in TLTG are retrospective and are based on small-sample studies, further, the results from such investigation have been inconsistent and even contradictory. Therefore, the safety and efficacy of linear stapling anastomosis has not been well resolved in these studies and remains to be confirmed by higher-level evidence. In view of this, a systematic review and meta-analysis will be conducted based on relevant published literature to further explore and compare the safety and efficacy of the linear stapler and circular stapler in TLTG, with the hope of providing a reference to help surgeons choose a suitable stapler.

2 Materials and methods

The protocol of the planned systematic review and meta-analysis was prepared in accordance with the recommendation from the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement,[15] and this systematic review and meta-analysis will be written in line with PRISMA statement.[16] In addition, this study protocol was registered with the international prospective register of systematic reviews PROSPERO (CRD42018111680).[17]

2.1 Literature-search strategy

Relevant studies will be searched on PubMed, Cochrane Library, Embase, CNKI, and Wanfang Databases in accordance with the population, intervention, control and outcomes (PICO) criteria from Jan-1990 to the actual start date. The studies comparing linear stapler with circular stapler for esophagojejunostomy in TLTG will be included. The following MeSH terms and their combinations will be searched in [Title/Abstract]: i) "*linear stapler*" OR "*overlap*" OR "*FEEA*" OR "*T-shaped*" OR "*π-shaped*" OR "*delta-shaped*"; ii) "*circular stapler*" OR "*OrVil™*" OR "*hemidouble stapling technique*" OR "*double stapling technique*"; iii) "*totally laparoscopic*"; iiii) "*total gastrectomy*". The related-articles function will be used to increase the search scope, and the computer search will be supplemented with manual screening of the reference lists of all retrieved studies, review articles and conference abstracts.

2.2 Inclusion criteria

(1) The subjects were the patients who had undergone esophagojejunostomy in totally laparoscopic total gastrectomy, and preoperative or postoperative histopathologic examination confirmed gastric cancer; (2) According to the different anastomosis methods used for esophagojejunostomy in digestive tract reconstruction, patients were divided into linear stapling

anastomosis and circular stapling anastomosis groups; (3) The study types were randomized controlled trials (RCTs), non-RCTs, or observational comparative studies; (4) The original literature should have terms including intraoperative conditions, postoperative specimens, postoperative recovery, postoperative complications, postoperative complications, or have at least one of these research data; (6) Pooled results can be formulated by the statistical index, such as odds ratio (OR), relative risk (RR), or weighted mean difference (WMD). (6) For multiple similar studies from the same research institution, a recent or higher quality study will be selected.

2.3 Exclusion criteria

(1) The literature including cases of open surgery or hand-assisted laparoscopic total gastrectomy; (2) The literature that did not respectively provide the data for linear stapler group and circular stapler group or the surgical method was not clearly stated in the literature; (3) The literature was a case report, case series, letters, review, or non-control study without control group; (4) The sample size was too small, and the number of cases was less than 20 cases; (5) Other treatments were differently performed between two groups during pre and post operation, and these treatments probably affected the observed outcome in the studies; (6) The literature was a repeated publication.

2.4 Study screening and selection

Any duplication will be identified and removed using the EndNote X8 reference management software (Clarivate Analytics, Thomson Place, Boston, USA). Under the pre-established inclusion and exclusion criteria, the titles and abstracts of all remaining literatures are carefully read and examined to exclude obviously unrelated documents. The full text of the screened literature will be deeply and carefully read to determine whether it is to be included. All steps will be independently

conducted and cross-checked by three reviewers, and all disagreements will be resolved by discussion with the senior authors (Xueqing Yao) until a consensus be reached. The detailed process of study selection will be displayed in detail in a PRISMA-compliant flow diagram (Figure 1).

2.5 Data extraction and outcomes of interest

Three reviewers will independently extract the data, and any discrepancy will be resolved by discussion until a consensus is reached. All extracted data will be filled in data extraction sheets created by Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington, USA). The main extracted information are as follows: (1) study characteristics (e.g: first author's name, year of publication, country of study, study design, study period, number of patients, number of patients with linear stapler, number of patients with circular stapler); (2) participant characteristics (e.g: age, sex, ethnicity, body mass index (BMI), cancer stage, American Society of Anesthesiologists (ASA) score); (3) primary outcomes: anastomotic leakage, anastomotic stricture, anastomotic hemorrhage, total postoperative complications; (4) secondary outcomes: first exhaust time after operation, first feeding time, total operation time, reconstruction time of digestive tract, estimated blood loss, lymph node harvest, the distance from the proximal margin of the tumor, postoperative hospital stay. Any missing information is supplemented by contacting the original author by telephone or e-mail.

2.6 Quality assessment

The quality of the studies will be independently scored by three reviewers using the Cochrane risk of bias tool or the Newcastle-Ottawa Quality Assessment Scale (NOS).[18] The methodological quality of randomized controlled trials will be assessed using the Cochrane risk of bias tool.[19] The methodological quality of non-random studies such as case-control and cohort studies will be

assessed by the NOS, which consists of three factors: patient selection, comparability of the study groups, and assessment of outcome. A score of 0–9 (allocated as stars) will be allocated to each study except for RCTs. RCTs and observational studies achieving six or more stars will be considered to be of high-quality studies. In cases where discrepancies arose, studies will be re-examined and a consensus will be reached through discussion.

2.7 Statistical analysis

All the meta-analyses will be performed using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). The weighted mean difference (WMD) and odds ratio (OR) will be used to compare continuous and dichotomous variables respectively, and all the results will be reported with 95% confidence intervals. For the literature reporting median and range of continuous variables, the mean and standard deviation (SD) will be extracted using the method described by Hozo et al.[20] Continuous variables that only provided quartiles or mean and SD could not be extracted will be eliminated. Assessment of statistical heterogeneity among the studies will be undertaken using the $\chi 2$ and I^2 statistical tests. Where there is no obvious statistical heterogeneity among the studies as denoted by a P value ≥ 0.1 or $I^2 \leq 50\%$, the fixed effect model will be used for meta-analysis. Conversely, in cases where statistical heterogeneity is observed among studies with a P value < 0.1 or $I^2 > 50\%$, a random effect model will be used for meta-analysis. If concerns for high heterogeneity (I^2 value >75% indicates high heterogeneity)[21] exist, a sensitivity analysis will be performed.

2.8 Assessment of publication bias

The potential publication bias will be investigated using funnel plots drawn by the STATA SE version 12.0 software. The publication bias will be assessed by visual inspection of the Begg's funnel

plots, whereby, if the standard error of logOR of each study is plotted against its logOR, an asymmetric plot suggests a possible publication bias.[22] In addition, the asymmetry of the funnel-plot will be assessed using the Egger linear regression test at the $p<0.10$ significance level.[23]

2.9 Subgroups analysis

To explore the potential heterogeneity, subgroup meta-analyses will be performed based on different characteristics of the patient (e.g: age, sex, ethnicity, BMI, cancer stage) as well as by study characteristics (e.g: country of study, study design, year of publication, study period, number of patients).

2.10 Sensitivity analysis

In order to ensure the robustness and reliability of evidence, sensitivity analysis will be performed to assess the effect of studies with a high risk of bias. The results will be compared to decide whether low-quality studies should be excluded based on sample size and quality assessment of studies or effect on pooled effective size. In addition, a leave-one-out sensitivity meta-analysis might be considered if a study involving a large number of patients was based on different types of studies.[24]

2.11 Patient and public involvement

Not applicable. Patient and public involvement will not be required because this proposed systematic review and meta-analysis is based on previously published data, which does not include intervention data on patients.

3 Discussion

Recent decades have witnessed significant advancements in the skills-set and the equipment for laparoscopic surgery advance. This has not only expanded the application scope of laparoscopic surgery in gastric cancer,[25 26] but has also lead to the transition of laparoscopic reconstruction of the digestive tract in gastric cancer from laparoscopic-assisted surgery to totally laparoscopic surgery.[6] However, the application of TLTG for total laparoscopic digestive tract reconstruction faces some difficulties due to its high technical requirements.[14 27] However, total laparoscopic digestive tract reconstruction after TLTG has obvious theoretical advantages.[28 29] For instance, the pneumoperitoneum provides a larger operation space for surgery and the multi-angle lens provides direct vision for operation to avoid damage. Therefore, TLTG is a promising technique for gastric cancer.

It is no doubt that the development of stapler technology has promoted the development of laparoscopic gastrointestinal operation, especially in TLTG. Presently, mechanical anastomosis for esophagojejunostomy in TLTG is mainly divided into two types: end-to-side anastomosis using the circular stapler and side-to-side/functional end-to-end anastomosis using the linear stapler. [6-8]

The circular stapling anastomosis method is divided into different methods according to the placement of the nail anvil: the traditional method of direct insertion, reverse anvil method and OrVil™ method.[30-32] However, in the first two methods, the main body of the stapler cannot enter the abdominal cavity through the trocar, which requires that the pneumoperitoneum be closed and a small auxiliary incision is often created, thereby reducing the fluency and efficiency of the operation. In addition, the difficult in operation of the esophageal purse suture and the placement of the nail anvil also limits the application of these two methods. Although the OrVil™ method does not require the placement of an anvil through the abdominal cavity, it requires the services of an anesthesiologist

and a special anvil placement device.[9] The price of the special device is high, and the extraction of the guide tube might cause intra-abdominal infection.[9 27 33]

Linear stapling anastomosis involves functional end-to-end anastomosis (FEEA method) as well as side-to-side anastomosis (Overlap method). [34] This technique is appropriate for total laparoscopic gastrectomy compared to using circular stapling anastomosis.[11 29 33] Based on the published literatures and the experience of our center, the linear stapler has the following advantages[28 35 36]: (1) linear stapler can be easily put into the abdominal cavity via a trocar and has a better visual field; (2) the operation of linear stapler is simple and convenient, and the requirement for the surgeon is lower compared to using a circular stapler; (3) the circular stapler with two rows of staples, but the linear stapler provides three rows of nail technology to theoretically improve the safety of the anastomosis. However, although some advantages have been reported for linear stapler, its application in laparoscopic total gastrectomy has some limitations such as [8 14]: (1) a longer stump of the esophagus is required which limits the incisal margin; (2) when the anastomosis plane is higher than the plane of esophageal hiatus, the operation is performed in a narrow thoracic cavity and the visual field is narrowed; (3) the pulling and folding of the jejunum arm might increase the tension in the anastomosis. Whether the possibly increased tension could increase the risk of anastomotic leak is an important topic needed to be resolved in this study. The discussed anastomotic methods have their advantages and disadvantages in the anastomosis of the esophagus between jejunum, and it is not clear which anastomosis technique is superior.[14] Further, no standard methods have been established to guide the selection.[37 38] Therefore, it is meaningful and necessary to conduct a systematic review and meta-analysis to provide a reference that could aid clinical surgeons in choosing a more appropriate alternative for their patients.

In this review, in order to collect all existing and available literature, RCTs and non-RCTs as well as observational studies will be included. Because of the novelty of this research topic, a few studies had been reported. However, the non-RCTs and observational studies might affect the quality of the evidence and lower the confidence level of the result. Besides, there are many factors such as different standards of choosing patients, different proficiency in laparoscopic techniques and different habits or methods of using the stapler by different surgeons in different regions, which might influence the results. Hence, in view of these, it is very important for this review to perform subgroup analysis and sensitivity analysis. Further analysis and explanations will be carried out in our review to ensure the robustness and reliability of the results.

In summary, this systematic review and meta-analysis will help to determine the differences in terms of safety and efficacy between linear stapler and circular stapler in TLTG. Furthermore, the findings of this study will not only help the surgeons in choosing the surgical methods, but also might benefit more patients in the future.

Abbreviations

LTG: laparoscopic total gastrectomy; TLTG: totally laparoscopic total gastrectomy; OTG: open total gastrectomy; LDG: laparoscopic distal gastrectomy; PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols; RCTs: randomized controlled trials; CNKI: China national knowledge infrastructure; ASA: American Society of Anesthesiologists; NOS: Newcastle-Ottawa Quality Assessment Scale; BMI: body mass index; FEEA: functional end-to-end anastomosis; WMD: weighted mean difference; SD: standard deviation; CI: confidence intervals.

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Not applicable

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Wrote the paper: Tianyou Liao, Leilei Deng. Study concept and design: Manzhao Ouyang, Xueqing Yao. Registered the protocol in the PROSPERO database: Tianyou Liao, Manzhao Ouyang. Preliminary literature search: Tianyou Liao, Leilei Deng. Corrected and revised manuscript: Manzhao Ouyang, Xueqing Yao. Approving current version of manuscript: Tianyou Liao, Leilei Deng, Xueqing Yao, Manzhao Ouyang.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Figure 1 Flow diagram of study selection

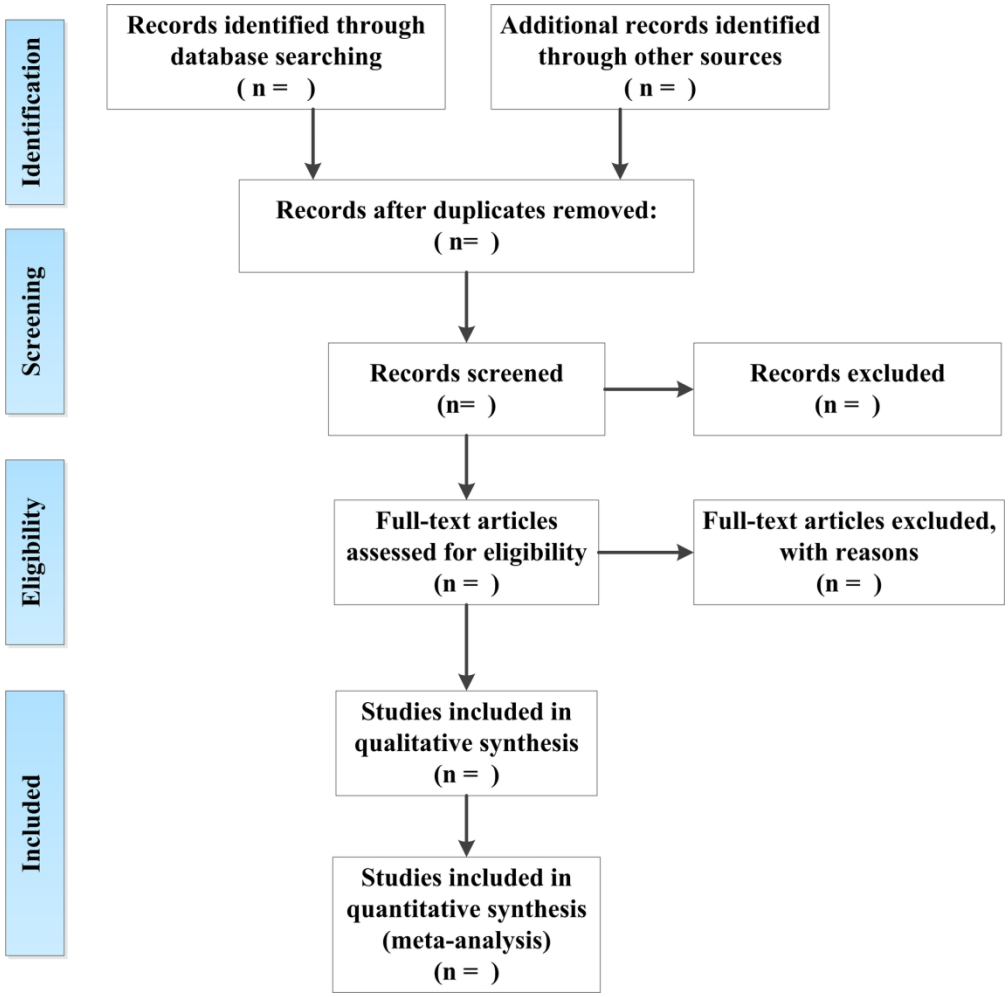

Figure 1 Flow diagram of study selection

162x160mm (300 x 300 DPI)

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☑	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☑	None
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☑	☐	45
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☑	☐	5-17
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☑	☐	282
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☑	None
Support					
Sources	5a	Indicate sources of financial or other support for the review	☑	☐	272
Sponsor	5b	Provide name for the review funder and/or sponsor	☑	☐	273-278
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☑	None
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☑	☐	58
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☑	☐	107
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report	☑	☐	118

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review			
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☑	☐	108-109; 114-117
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☑	☐	111-114
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☑	☐	138
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☑	☐	138
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☑	☐	147
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☐	☑	None
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☑	☐	147
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☑	☐	160; 183
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐	☑	None
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☑	☐	170
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☑	☐	189; 194
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☑	None
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☑	☐	183
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☑	None

BMJ Open

Comparison of the safety and efficacy between linear stapler and circular stapler in totally laparoscopic total gastrectomy: protocol for a systematic review and meta-analysis

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Comparison of the safety and efficacy between linear stapler and circular stapler in totally laparoscopic total gastrectomy: protocol for a systematic review and meta-analysis

Running Head: Protocol for a meta-analysis of linear versus circular stapler in TLTG

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Abstract

Introduction: Total gastrectomy is often recommended for upper body gastric cancer, and totally laparoscopic total gastrectomy (TLTG) is deemed to be a promising surgical method with the well-known advantages such as less invasion and fast recovery. However, the anastomosis between esophagus and jejunum is the difficulty of TLTG. Although staplers have promoted the development of TLTG, the choice of suitable staplers to complete esophagojejunostomy is controversial and unclear. Therefore, a higher level of research evidence is needed to compare the two types of staplers in terms of safety and efficacy for esophagojejunostomy in TLTG among patients with gastric cancer.

Methods and analysis: PubMed, Embase, Cochrane Library, CNKI and Wanfang Databases will be comprehensively searched from Jan-1990 to Jul-2019. All eligible RCTs, non-RCTs, or observational studies comparing the two types of staplers will be included. A meta-analysis will be performed using Review Manager 5.3 software to compare the safety and efficacy of linear and circular staplers for esophagojejunostomy in TLTG. The primary outcomes are anastomotic leakage, anastomotic stricture, anastomotic hemorrhage. The secondary outcomes include time to first instance of passing gas after surgery, first feeding time, total operation time, reconstruction time, estimated blood loss. The heterogeneity of this study will be assessed by P values and I^2 statistic. Subgroup analyses and sensitivity analyses will be used to explore and explain the heterogeneity. The risk of bias will be assessed using the Cochrane tool or the Newcastle-Ottawa Quality Assessment Scale.

Ethics and dissemination: Ethical approval will not be required because this proposed systematic

review and meta-analysis is based on previously published data, which does not include intervention data on patients. The findings of this study will be submitted to a peer-reviewed journal and will be presented at a relevant congress.

PROSPERO registration number: CRD42018111680.

Keywords: linear stapler; circular stapler; totally laparoscopic total gastrectomy; esophagojejunostomy

Strengths and limitations of this study

(1) To our best knowledge, this review will be the first systematic review and meta-analysis to compare the safety and efficacy of the linear stapler and circular staplers in TLTG.

(2) The study selection, data extraction, and quality assessment of the studies will be performed by three independent reviewers.

(3) Subgroup analyses and sensitivity analyses will be used to explore and explain the heterogeneity.

(4) Some observational studies might be included in this study, which might affect the quality of the data.

(5) There might be some selection bias in this systematic review and meta-analysis, because the resource databases are limited to English and Chinese language.

1 Introduction

Gastric cancer is a common malignant tumor of the digestive tract, and its morbidity and mortality ranked 5th and 3rd respectively among the global malignant tumors.[1] Although the overall incidence of gastric cancer has been decreasing worldwide, the incidence of upper body gastric cancer has been on an increasing trend.[2] [3] Radical resection is the only curative modality recommended for primary treatment of patients with resectable gastric cancer, and total gastrectomy is often performed for upper body gastric cancer.[3] [4] Laparoscopic technique is one of the main development direction of surgical treatment for gastric cancer. The results of a multi-center retrospective cohort study have shown that laparoscopic total gastrectomy (LTG) could achieve comparable oncological outcomes to open total gastrectomy (OTG).[5] Furthermore, with the development of new laparoscopic equipments and the accumulation of advanced experience in the application of laparoscopic techniques, laparoscopic surgery for gastric cancer has undergone a technological transition from laparoscopic-assisted surgery to totally laparoscopic surgery which is less invasive and expedites postoperative recovery.[6]

However, the anastomosis and reconstruction of esophagojejunostomy is the focal point and difficulty of totally laparoscopic total gastrectomy (TLTG).[6] Presently, the two commonly used anastomosis methods for esophagojejunostomy are circular stapler anastomosis and linear stapler anastomosis.[6-8] Considering the characteristics of laparoscopic surgery, traditional circular anastomosis has certain inherent limitations. For example, the circular stapler cannot be placed through a trocar, and it needs to be placed in the abdominal cavity through a small assisted incision in the abdomen, thereby reducing the benefit of laparoscopic surgery. Although OrVil™ does not pass through the abdominal cavity, a top-down placement method is required, but the operation

requires an anesthesiologist to cooperate.[9] Compared with the circular stapler, linear stapler has some advantages in esophagojejunostomy.[10] For example, it can easily enter the abdominal cavity through the trocar, without purse-string suture, and the used instrument is easy to operate. The primary disadvantage of linear anastomosis is the need for a long-enough esophageal stump for anastomosis, which limits the surgical margin and could increase the tension of the anastomosis. For this reason, some scholars consider that linear anastomosis is not appropriate for patients with tumors located in the upper stomach or close to the esophago-gastric junction or tumors with esophageal invasion.[11 12] A meta-analyses comparing linear anastomosis with circular anastomosis in laparoscopic distal gastrectomy (LDG) suggested that linear anastomosis is better than circular anastomosis in LDG[13]. However, considering the differences between TLTG and LDG in terms of surgical methods, surgical objects and surgical difficulties, this conclusion cannot be applied to guide the implementation of TLTG.

Therefore, the choice of staplers for complete esophagojejunostomy of TLTG is still an unclear and controversial topic.[7 8 14] Majority of the previous comparisons on contrasting linear and circular stapling anastomosis for esophagojejunostomy in TLTG are retrospective and are based on small-sample studies, further, the results from such investigation have been inconsistent and even contradictory. Therefore, the safety and efficacy of linear stapling anastomosis has not been well resolved in these studies and remains to be confirmed by higher-level evidence. In view of this, a systematic review and meta-analysis will be conducted based on relevant published literature to further explore and compare the safety and efficacy of the linear stapler and circular stapler in TLTG, with the hope of providing a reference to help surgeons choose a suitable stapler.

2 Materials and methods

The protocol of the planned systematic review and meta-analysis was prepared in accordance with the recommendation from the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement,[15] and this systematic review and meta-analysis will be written in line with PRISMA statement.[16] In addition, this study protocol was registered with the international prospective register of systematic reviews PROSPERO (CRD42018111680).[17]

2.1 Literature-search strategy

Relevant studies will be searched on PubMed, Cochrane Library, Embase, CNKI, and Wanfang Databases in accordance with the population, intervention, control and outcomes (PICO) criteria from Jan-1990 to Jul-2019. The studies comparing linear stapler with circular stapler for esophagojejunostomy in TLTG will be included. The following MeSH terms and their combinations will be searched in [Title/Abstract]: i) "*linear stapler*" OR "*overlap*" OR "*FEEA*" OR "*functional end-to-end anastomosis*" OR "*T-shaped*" OR "*π-shaped*" OR "*delta-shaped*"; ii) "*circular stapler*" OR "*OrVil*^{TM}" OR "*hemidouble stapling technique*" OR "*double stapling technique*"; iii) "*totally laparoscopic*"; iiii) "*total gastrectomy*". The related-articles function will be used to increase the search scope, and the computer search will be supplemented with manual screening of the reference lists of all retrieved studies, review articles and conference abstracts.

2.2 Inclusion criteria

(1) The subjects were the patients who had undergone esophagojejunostomy in totally laparoscopic total gastrectomy, and preoperative or postoperative histopathologic examination confirmed gastric cancer; (2) According to the different anastomosis methods used for esophagojejunostomy in digestive tract reconstruction, patients were divided into linear stapling

anastomosis and circular stapling anastomosis groups; (3) The study types were randomized controlled trials (RCTs), non-RCTs, or observational comparative studies; (4) The original literature should have terms including intraoperative conditions, postoperative specimens, postoperative recovery, postoperative complications, postoperative complications, or have at least one of these research data; (6) Pooled results can be formulated by the statistical index, such as odds ratio (OR), relative risk (RR), or weighted mean difference (WMD). (6) For multiple similar studies from the same research institution, a recent or higher quality study will be selected.

2.3 Exclusion criteria

(1) The literature including cases of open surgery or hand-assisted laparoscopic total gastrectomy; (2) The literature that did not respectively provide the data for linear stapler group and circular stapler group or the surgical method was not clearly stated in the literature; (3) The literature was a case report, case series, letters, review, or non-control study without control group; (4) The sample size was too small, and the number of cases was less than 20 cases. The studies with fewer than 20 cases are usually considered small-sample studies and were excluded by authors in some published meta-analysis articles.[18] (5) Other treatments were differently performed between two groups during pre and post operation, and these treatments probably affected the observed outcome in the studies; (6) The literature was a repeated publication.

2.4 Study screening and selection

Any duplication will be identified and removed using the EndNote X8 reference management software (Clarivate Analytics, Thomson Place, Boston, USA). Under the pre-established inclusion and exclusion criteria, the titles and abstracts of all remaining literatures are carefully read and

examined to exclude obviously unrelated documents. The full text of the screened literature will be deeply and carefully read to determine whether it is to be included. All steps will be independently conducted and cross-checked by three reviewers, and all disagreements will be resolved by discussion with the senior authors (Xueqing Yao) until a consensus be reached. The detailed process of study selection will be displayed in detail in a PRISMA-compliant flow diagram (Figure 1).

2.5 Data extraction and outcomes of interest

Three reviewers will independently extract the data, and any discrepancy will be resolved by discussion until a consensus is reached. All extracted data will be filled in data extraction sheets created by Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington, USA). The main extracted information are as follows: (1) study characteristics (e.g: first author's name, year of publication, country of study, study design, study period, number of patients, number of patients with linear stapler, number of patients with circular stapler); (2) participant characteristics (e.g: age, sex, ethnicity, body mass index (BMI), cancer stage, American Society of Anesthesiologists (ASA) score); (3) primary outcomes: anastomotic leakage, anastomotic stricture, anastomotic hemorrhage, total postoperative complications; (4) secondary outcomes: time to first instance of passing gas after surgery, first feeding time, total operation time, reconstruction time of digestive tract, estimated blood loss, lymph node harvest, the distance from the proximal margin of the tumor, postoperative hospital stay. Any missing information is supplemented by contacting the original author by telephone or e-mail.

2.6 Quality assessment

The quality of the studies will be independently scored by three reviewers using the Cochrane

risk of bias tool or the Newcastle-Ottawa Quality Assessment Scale (NOS).[19] The methodological quality of randomized controlled trials will be assessed using the Cochrane risk of bias tool.[20] The methodological quality of non-random studies such as case-control and cohort studies will be assessed by the NOS, which consists of three factors: patient selection, comparability of the study groups, and assessment of outcome. A score of 0–9 (allocated as stars) will be allocated to each study except for RCTs. RCTs and observational studies achieving six or more stars will be considered to be of high-quality studies. In cases where discrepancies arose, studies will be re-examined and a consensus will be reached through discussion.

2.7 Statistical analysis

All the meta-analyses will be performed using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). The weighted mean difference (WMD) and odds ratio (OR) will be used to compare continuous and dichotomous variables respectively, and all the results will be reported with 95% confidence intervals. For the literature reporting median and range of continuous variables, the mean and standard deviation (SD) will be extracted using the method described by Hozo et al.[21] Continuous variables that only provided quartiles or mean and SD could not be extracted will be eliminated. Assessment of statistical heterogeneity among the studies will be undertaken using the $\chi 2$ and I^2 statistical tests. Where there is no obvious statistical heterogeneity among the studies as denoted by a P value ≥ 0.1 or $I^2 \leq 50\%$, the fixed effect model will be used for meta-analysis. Conversely, in cases where statistical heterogeneity is observed among studies with a P value < 0.1 or $I^2 > 50\%$, a random effect model will be used for meta-analysis. If concerns for high heterogeneity (I^2 value >75% indicates high heterogeneity)[22] exist, a sensitivity analysis will be performed.

2.8 Assessment of publication bias

The potential publication bias will be investigated using funnel plots drawn by the STATA SE version 12.0 software. The publication bias will be assessed by visual inspection of the Begg's funnel plots, whereby, if the standard error of logOR of each study is plotted against its logOR, an asymmetric plot suggests a possible publication bias.[23] In addition, the asymmetry of the funnel-plot will be assessed using the Egger linear regression test at the $p<0.10$ significance level.[24]

2.9 Subgroups analysis

To explore the potential heterogeneity, subgroup meta-analyses will be performed based on different characteristics of the patient (e.g: age, sex, ethnicity, BMI, cancer stage) as well as by study characteristics (e.g: country of study, study design, year of publication, study period, number of patients).

2.10 Sensitivity analysis

In order to ensure the robustness and reliability of evidence, sensitivity analysis will be performed to assess the effect of studies with a high risk of bias. The results will be compared to decide whether low-quality studies should be excluded based on sample size and quality assessment of studies or effect on pooled effective size. In addition, a leave-one-out sensitivity meta-analysis might be considered if a study involving a large number of patients was based on different types of studies.[25]

2.11 Patient and public involvement

Not applicable. Patient and public involvement will not be required because this proposed

systematic review and meta-analysis is based on previously published data, which does not include intervention data on patients.

2.12 Ethics and dissemination

Ethical approval will not be required because this proposed systematic review and meta-analysis is based on previously published data, which does not include intervention data on patients. The findings of this study will be submitted to a peer-reviewed journal and will be presented at a relevant congress.

3 Discussion

Recent decades have witnessed significant advancements in the skills-set and the equipment for laparoscopic surgery advance. This has not only expanded the application scope of laparoscopic surgery in gastric cancer,[26 27] but has also lead to the transition of laparoscopic reconstruction of the digestive tract in gastric cancer from laparoscopic-assisted surgery to totally laparoscopic surgery.[6] However, the application of TLTG for total laparoscopic digestive tract reconstruction faces some difficulties due to its high technical requirements.[14 28] However, total laparoscopic digestive tract reconstruction after TLTG has obvious theoretical advantages.[29 30] For instance, the pneumoperitoneum provides a larger operation space for surgery and the multi-angle lens provides direct vision for operation to avoid damage. Therefore, TLTG is a promising technique for gastric cancer.

It is no doubt that the development of stapler technology has promoted the development of laparoscopic gastrointestinal operation, especially in TLTG. Presently, mechanical anastomosis for esophagojejunostomy in TLTG is mainly divided into two types: end-to-side anastomosis using the circular stapler and side-to-side/functional end-to-end anastomosis using the linear stapler. [6-8]

The circular stapling anastomosis method is divided into different methods according to the placement of the nail anvil: the traditional method of direct insertion, reverse anvil method and OrVil™ method.[31-33] However, in the first two methods, the main body of the stapler cannot enter the abdominal cavity through the trocar, which requires that the pneumoperitoneum be closed and a small auxiliary incision is often created, thereby reducing the fluency and efficiency of the operation. In addition, the difficult in operation of the esophageal purse suture and the placement of the nail anvil also limits the application of these two methods. Although the OrVil™ method does not require the placement of an anvil through the abdominal cavity, it requires the services of an anesthesiologist and a special anvil placement device.[9] The price of the special device is high, and the extraction of the guide tube might cause intra-abdominal infection.[9 28 34]

Linear stapling anastomosis involves functional end-to-end anastomosis (FEEA method) as well as side-to-side anastomosis (Overlap method). [35] This technique is appropriate for total laparoscopic gastrectomy compared to using circular stapling anastomosis.[11 30 34] Based on the published literatures and the experience of our center, the linear stapler has the following advantages[29 36 37]: (1) linear stapler can be easily put into the abdominal cavity via a trocar and has a better visual field; (2) the operation of linear stapler is simple and convenient, and the requirement for the surgeon is lower compared to using a circular stapler; (3) the circular stapler with two rows of staples, but the linear stapler provides three rows of nail technology to theoretically improve the safety of the anastomosis. However, although some advantages have been reported for linear stapler, its application in laparoscopic total gastrectomy has some limitations such as [8 14]: (1) a longer stump of the esophagus is required which limits the incisal margin; (2) when the anastomosis plane is higher than the plane of esophageal hiatus, the operation is performed in a narrow thoracic cavity and the visual field is

narrowed; (3) the pulling and folding of the jejunum arm might increase the tension in the anastomosis. Whether the possibly increased tension could increase the risk of anastomotic leak is an important topic needed to be resolved in this study. The discussed anastomotic methods have their advantages and disadvantages in the anastomosis of the esophagus between jejunum, and it is not clear which anastomosis technique is superior.[14] Further, no standard methods have been established to guide the selection.[38 39] Therefore, it is meaningful and necessary to conduct a systematic review and meta-analysis to provide a reference that could aid clinical surgeons in choosing a more appropriate alternative for their patients.

In this review, in order to collect all existing and available literature, RCTs and non-RCTs as well as observational studies will be included. Because of the novelty of this research topic, a few studies had been reported. However, the non-RCTs and observational studies might affect the quality of the evidence and lower the confidence level of the result. Besides, there are many factors such as different standards of choosing patients, different proficiency in laparoscopic techniques and different habits or methods of using the stapler by different surgeons in different regions, which might influence the results. Hence, in view of these, it is very important for this review to perform subgroup analysis and sensitivity analysis. Further analysis and explanations will be carried out in our review to ensure the robustness and reliability of the results.

In summary, this systematic review and meta-analysis will help to determine the differences in terms of safety and efficacy between linear stapler and circular stapler in TLTG. Furthermore, the findings of this study will not only help the surgeons in choosing the surgical methods, but also might benefit more patients in the future.

Abbreviations

LTG: laparoscopic total gastrectomy; TLTG: totally laparoscopic total gastrectomy; OTG: open total gastrectomy; LDG: laparoscopic distal gastrectomy; PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols; RCTs: randomized controlled trials; CNKI: China national knowledge infrastructure; ASA: American Society of Anesthesiologists; NOS: Newcastle-Ottawa Quality Assessment Scale; BMI: body mass index; FEEA: functional end-to-end anastomosis; WMD: weighted mean difference; SD: standard deviation; CI: confidence intervals.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Wrote the paper: Tianyou Liao, Leilei Deng. Study concept and design: Manzhao Ouyang, Xueqing Yao. Registered the protocol in the PROSPERO database: Tianyou Liao, Manzhao Ouyang. Preliminary literature

search: Tianyou Liao, Leilei Deng. Corrected and revised manuscript: Manzhao Ouyang, Xueqing Yao. Approving current version of manuscript: Tianyou Liao, Leilei Deng, Xueqing Yao, Manzhao Ouyang.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Figure 1 Flow diagram of study selection

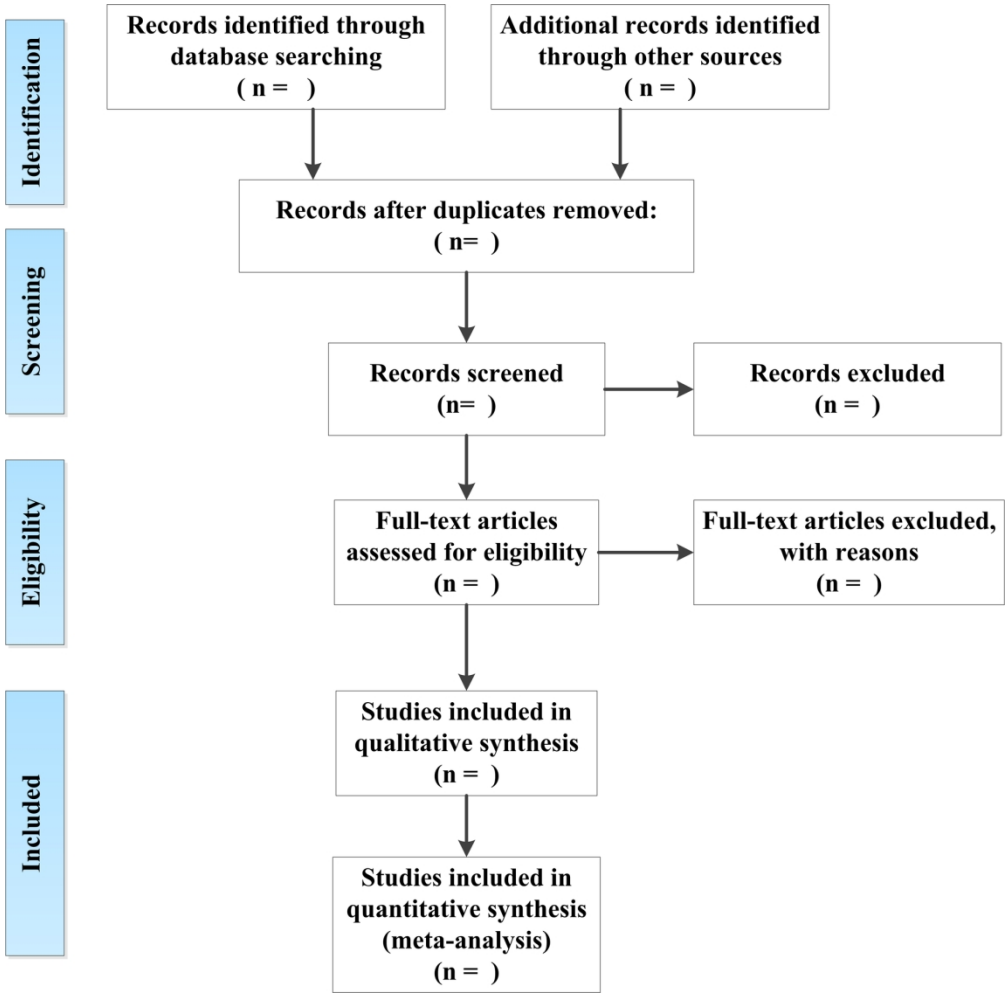

Figure 1 Flow diagram of study selection

162x160mm (300 x 300 DPI)

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☑	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☑	None
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☑	☐	43
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☑	☐	5-17
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☑	☐	288
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☑	None
Support					
Sources	5a	Indicate sources of financial or other support for the review	☑	☐	278
Sponsor	5b	Provide name for the review funder and/or sponsor	☑	☐	279-284
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☑	None
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☑	☐	56
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☑	☐	105
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report	☑	☐	116

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review			
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☑	☐	106-107; 113-115
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☑	☐	109-113
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☑	☐	138
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☑	☐	138
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☑	☐	147
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☐	☑	None
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☑	☐	147
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☑	☐	161; 184
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐	☑	None
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☑	☐	171
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☑	☐	190; 195
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☑	None
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☑	☐	184
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☑	None