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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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Manuscripts

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4 **Comparison of the safety and efficacy between linear stapler and circular stapler in totally**
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6 **laparoscopic total gastrectomy: protocol for a systematic review and meta-analysis**
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9 **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

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4 interventions on patients.
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6 **PROSPERO registration number:** CRD42018111680.
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9 **Keywords:** linear stapler; circular stapler; totally laparoscopic total gastrectomy;
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11 esophagojejunostomy
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16 **Strengths and limitations of this study**

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18 (1) To our best knowledge, this review will be the first systematic review and meta-analysis to
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20 compare the safety and efficacy of the linear stapler and circular staplers in TLTG.
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23 (2) The study selection, data extraction, and quality assessment of the studies will be performed by
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25 three independent reviewers.
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28 (3) Subgroup analyses and sensitivity analyses will be used to explore and explain the heterogeneity.
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30 (4) Some observational studies might be included in this study, and might affect the quality of the
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32 evidence.
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35 (5) There might be some selection bias in this systematic review and meta-analysis, because the
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37 retrieved databases are limited to English and Chinese database.
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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 OrVilTM does not pass through the abdominal cavity, the top-down placement method is required, but the operation requires

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

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22 Therefore, the choice of the staplers to use for complete esophagojejunostomy of TLTG is still
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24 an unclear and controversial topic.^{7 8 13} Previous reports on contrasting linear and circular stapling
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26 anastomosis for esophagojejunostomy in TLTG mostly are retrospective and are based on
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28 small-sample studies, further, there exists some contradictory results in the different studies.
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30 Therefore, the safety and efficacy of linear stapling anastomosis has not been well resolved in these
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32 studies and remains to be confirmed by higher-level evidence. In view of this, a systematic review
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34 and meta-analysis will be conducted based on relevant published literature to further explore and
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36 compare the safety and efficacy of the linear stapler and circular stapler in TLTG, with the hope of
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38 providing a reference to help surgeons choose a better stapler.
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48 **2 Materials and methods**

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

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4 or weighted mean difference (WMD). (6) For multiple documents from the same research institution,
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6 a recent or higher quality research will be selected.
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9 **2.3 Exclusion criteria**

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11 (1) The literature included cases of open surgery or hand-assisted laparoscopic total gastrectomy; (2)
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13 The literature that did not respectively provide the data for linear stapler group and circular stapler
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15 group or the surgical method was not clearly stated in the literature; (3) The literature was a case
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17 report, case series, letters, review, or non-control study without control group; (4) The sample size
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19 was too small, and the number of cases was less than 20 cases; (5) Other treatments were differently
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21 performed between two groups during pre and post operation, and these treatments probably
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23 affected the observed outcome of the studies; (6) The literature was a repeated publication.
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30 **2.4 Study screening and selection**

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32 Any duplication will be found and removed using EndNote X8 reference management software
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34 (Clarivate Analytics, Thomson Place, Boston, USA). Under the pre-established inclusion and
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36 exclusion criteria, the titles and abstracts of all remaining literatures are carefully read and examined
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38 to exclude obviously unrelated documents. The full text of screened literature will be then deeply and
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40 carefully read to determine whether it is to be included. All steps will be independently conducted
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42 and cross-checked by three reviewers, and all disagreements are resolved by discussion with the
43
44 senior authors (Xueqing Yao) until a consensus be reached. The detailed process of study selection
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46 will be recorded in detail in a PRISMA-compliant flow diagram (Figure 1).
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53 **2.5 Data extraction and outcomes of interest**

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55 Three reviewers will independently extract the data, and any discrepancy will be resolved by
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57 discussion until a consensus reached. All extracted data will be filled in data extraction sheets created
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4 by Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington, USA). The main extracted
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6 information are as follows: (1) study characteristics (e.g: first author's name, year of publication,
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8 country of study, study design, study period, number of patients, number of patients with linear
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10 stapler, number of patients with circular stapler, etc); (2) participant characteristics (e.g: age, sex,
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12 ethnicity, body mass index (BMI), cancer stage, American Society of Anesthesiologists (ASA) score
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14 etc); (3) primary outcomes: anastomotic leakage, anastomotic stricture, anastomotic haemorrhage,
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16 total postoperative complications; (4) secondary outcomes: first exhaust time after operation, first
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18 feeding time, total operation time, reconstruction time of digestive tract, estimated blood loss, lymph
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20 node harvest, the distance from the proximal margin of the tumor, postoperative hospital stay. Any
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22 missing information is supplemented by contacting the original author by telephone or e-mail.
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30 **2.6 Quality assessment**

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32 Study quality will be independently scored by three reviewers using the Cochrane risk of bias
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34 tool or the Newcastle-Ottawa Quality Assessment Scale (NOS).¹⁷ The methodological quality of
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36 randomized controlled trials will be assessed by the Cochrane risk of bias tool.¹⁸ The methodological
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38 quality of nonrandom studies as case-control and cohort studies will be assessed by the NOS, which
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40 consists of three factors: patient selection, comparability of the study groups, and assessment of
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42 outcome. A score of 0–9 (allocated as stars) be allocated to each study except for RCTs. RCTs and
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44 observational studies achieving six or more stars be considered to be of high-quality studies. In cases
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46 where discrepancies arose, studies will be re-examined and a consensus will be reached through
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48 discussion.
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55 **2.7 Statistical analysis**

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

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4 esophagojejunostomy in TLTG is mainly divided into two types: end-to-side anastomosis using the
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6 circular stapler and side-to-side/ functional end-to-end anastomosis using the linear stapler. ⁶⁻⁸
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9 The circular stapling anastomosis method is divided into different methods according to the
10 placement of the nail anvil: the traditional method of direct insertion, reverse anvil method and
11 OrVil™ method.²⁹⁻³¹ However, in the first two methods, the main body of the stapler cannot enter
12 the abdominal cavity through the trocar, the pneumoperitoneum must be closed and a small auxiliary
13 incision is often needed, thereby reducing the fluency of the operation. In addition, the difficult in
14 operation of the esophageal purse suture and the placement of the nail anvil also limits the
15 application of these two methods. While the OrVil™ method does not require the placement of an
16 anvil through the abdominal cavity, which has certain disadvantages that the OrVil™ method
17 requires the cooperation of an anesthesiologist and requires a special anvil placement device.⁹ The
18 price of the special device is high, and the extraction of the guide tube might cause intra-abdominal
19 infection.^{9 26 32}
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38 Linear stapling anastomosis involves functional end-to-end anastomosis (FEEA method) as well
39 as side-to-side anastomosis (Overlap method) ³³ and has absolute advantage in total laparoscopic
40 gastrectomy compared with the disadvantages of circular stapling anastomosis.^{11 28 32} Based on the
41 published literatures and the experience of our center, the advantages of linear stapler are mainly
42 reflected in that^{27 34 35}: (1) linear stapler can be more easily accessed into the abdominal cavity via
43 trocar and has a better visual field; (2) the operation of linear stapler is simple and convenient, and
44 the requirement for the surgeon is lower than that of using a circular stapler; (3) composed with the
45 circular stapler with two rows of staples, the line stapler can use three rows of nail technology to
46 theoretically improve the safety of the anastomosis. However, although some advantages have been
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4 reported for linear stapler, its application in laparoscopic total gastrectomy has some limitations such
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6 as ^{8 13}: (1) retaining a longer stump of the esophagus is required which lead to limited incisal margin;
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9 (2) when the anastomosis plane is higher than the plane of esophageal hiatus, the operation is
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11 performed in a narrow thoracic cavity and the visual field is easily restricted; (3) the pulling and
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13 folding of the jejunum arm might increase the tension of the anastomosis. Whether the possibly
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15 increased tension could increase the risk of anastomotic leak is an important topic needed to be
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17 resolved in this study. The discussed anastomotic methods have their advantages and disadvantages
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19 in the anastomosis of the esophagus between jejunum, and it is not clear which anastomosis
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21 technique is superior.¹³ Further, no standard methods have been established to guide the selection.³⁶
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27 ³⁷ Therefore, it is meaningful and necessary to conduct a systematic review and meta-analysis to
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29 provide a reference that could aid clinical surgeons in choosing a more appropriate alternative for
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31 their patients.
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35 In this review, in order to collect all existing and available literature, RCTs and non-RCTs as
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37 well as observational studies will be included. Because of the novelty of this research topic, a few
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39 studies had been reported. However, the non-RCTs and observational studies might affect the quality
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41 of the evidence and lower the confidence level of the result. Besides, there are many
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43 influencing factors such as different standards in choosing patients, different proficiency in
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45 laparoscopic techniques and different habits or methods of using the stapler by different surgeons in
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47 different regions, which might have impacted the results. Hence, in view of these, it is very important
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49 for this review to perform subgroup analysis and sensitivity analysis. Further analysis and
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51 explanations will be carried out in our studies to ensure the robustness and reliability of the results.
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58 In summary, this systematic review and meta-analysis will help to determine the difference in
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4 terms of safety and efficacy between linear stapler and circular stapler in TLTG. Furthermore, the
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6 findings of this study will not only help the surgeons in choosing the surgical methods, but also might
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8 benefit more patients in the future.
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11 12 13 14 **Abbreviations**

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16 LTG: laparoscopic total gastrectomy; TLTG: totally laparoscopic total gastrectomy; OTG: open total gastrectomy;
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18 PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols; RCTs: randomized
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20 controlled trials; CNKI: China national knowledge infrastructure; ASA: American Society of Anesthesiologists;
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22 NOS: Newcastle-Ottawa Quality Assessment Scale; BMI: body mass index; FEEA: functional end-to-end
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24 anastomosis; WMD: weighted mean difference; SD: standard deviation; CI: confidence intervals.
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31
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42
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44
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46
47 (FSGSPZD135051).
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52 **Availability of data and materials**

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

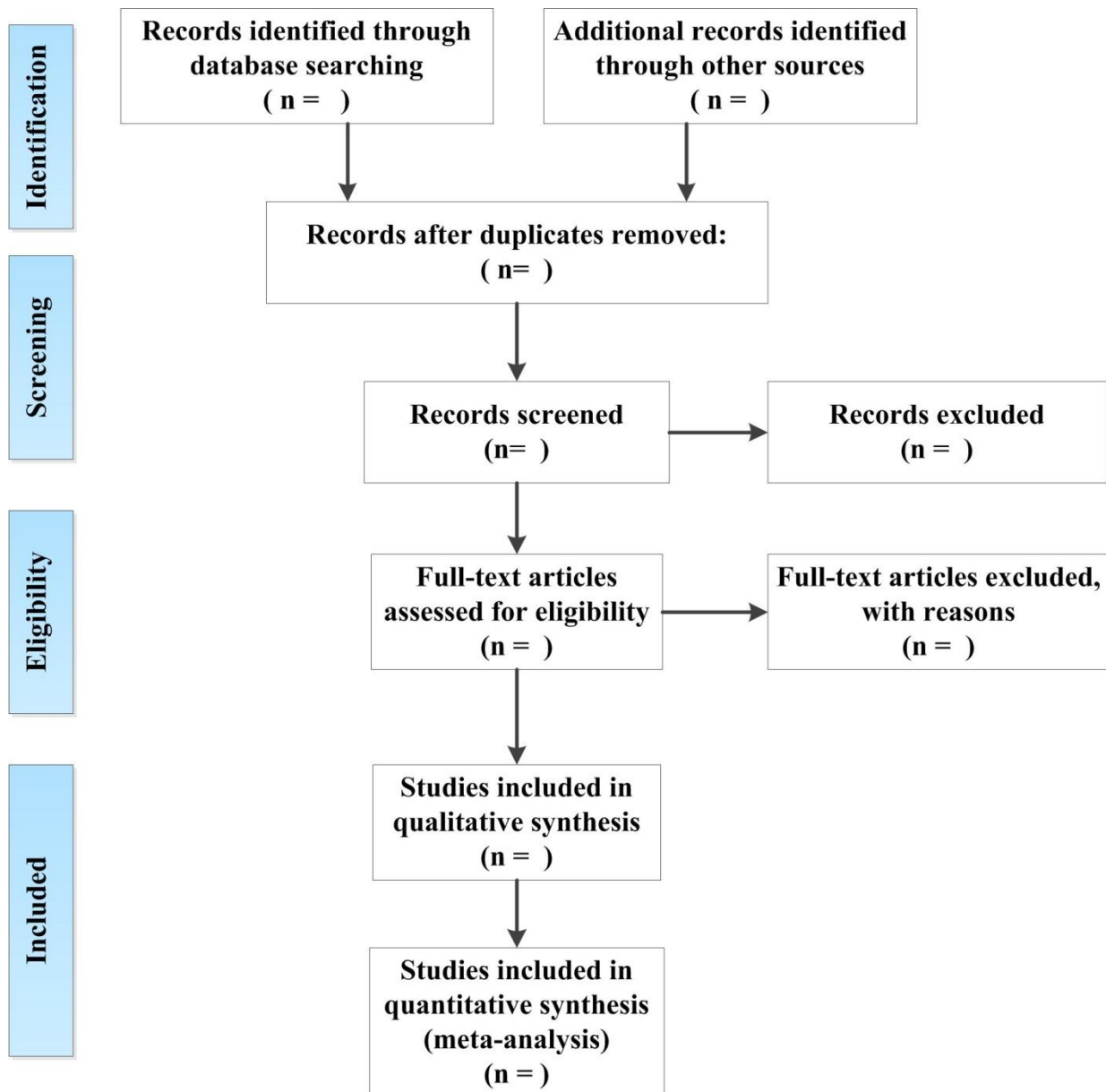
The authors declare that they have no competing interests.

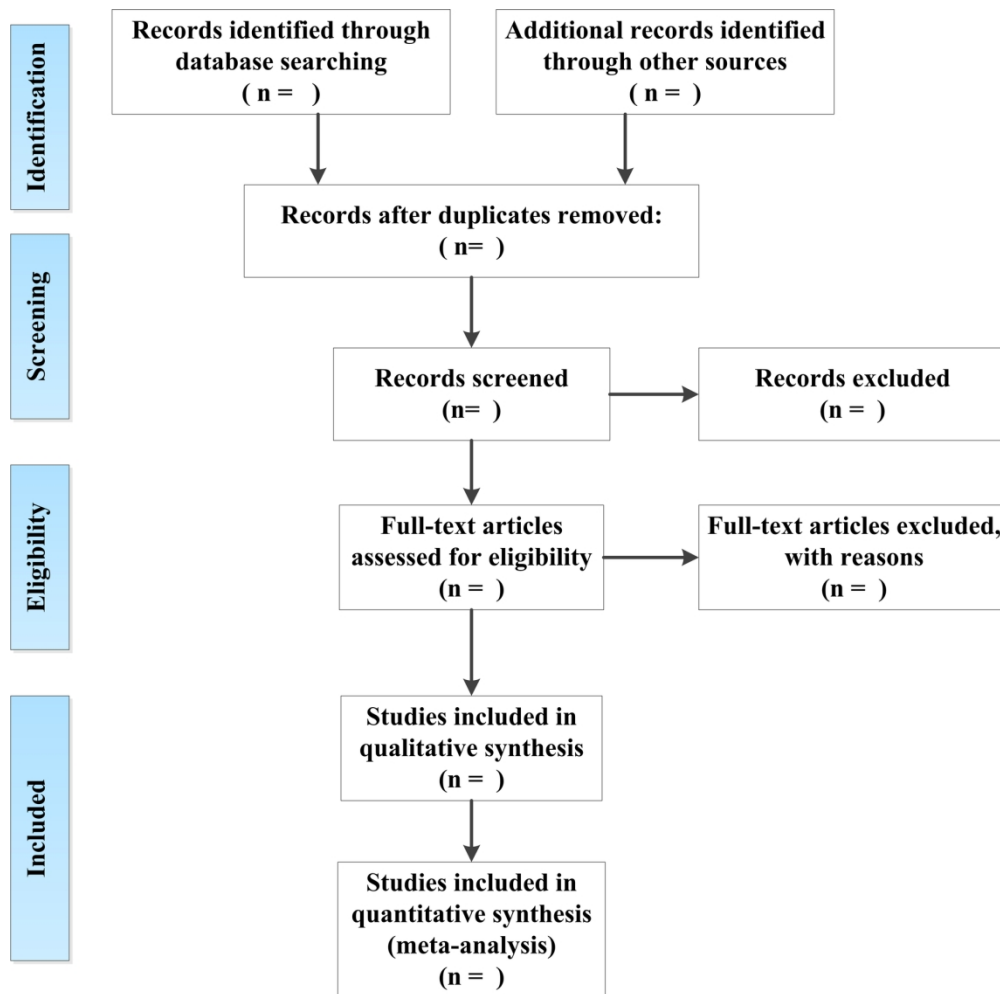
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Figure 1 Flow diagram of study selection





162x160mm (300 x 300 DPI)

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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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Gastroenterology and hepatology, Oncology, Surgery
Keywords:	linear stapler, circular stapler, totally laparoscopic total gastrectomy, esophagojejunostomy

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Manuscripts

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4 1 **Comparison of the safety and efficacy between linear stapler and circular stapler in totally**
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6 2 **laparoscopic total gastrectomy: protocol for a systematic review and meta-analysis**

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9 3 **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.

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4 42 **Ethics and dissemination:** Ethical approval will not be required because this proposed systematic
5
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7 43 review and meta-analysis is based on previously published data, which does not include intervention
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9 44 data on patients.

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11
12 45 **PROSPERO registration number:** CRD42018111680.

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15 46 **Keywords:** linear stapler; circular stapler; totally laparoscopic total gastrectomy;
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18 47 esophagojejunostomy

19 20 21 48 **Strengths and limitations of this study**

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24 49 (1) To our best knowledge, this review will be the first systematic review and meta-analysis to
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26 50 compare the safety and efficacy of the linear stapler and circular staplers in TLTG.

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28
29 51 (2) The study selection, data extraction, and quality assessment of the studies will be performed by
30
31
32 52 three independent reviewers.

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34
35 53 (3) Subgroup analyses and sensitivity analyses will be used to explore and explain the heterogeneity.

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38 54 (4) Some observational studies might be included in this study, which might affect the quality of the
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41 55 data.

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44 56 (5) There might be some selection bias in this systematic review and meta-analysis, because the
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47 57 resource databases are limited to English and Chinese language.
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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 OrVilTM does not pass through the abdominal cavity, a top-down placement method is required, but the operation

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4 80 requires an anesthesiologist to cooperate.⁹ Compared with the circular stapler, linear stapler has some
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6 81 advantages in esophagojejunostomy.¹⁰ For example, it can easily enter the abdominal cavity through
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9 82 the trocar, without purse-string suture, and the used instrument is easy to operate. The primary
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12 83 disadvantage of linear anastomosis is the need for a long-enough esophageal stump for anastomosis,
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14 84 which limits the surgical margin and could increase the tension of the anastomosis. For this reason,
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17 85 some scholars consider that linear anastomosis is not appropriate for patients with tumors located in
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19
20 86 the upper stomach or close to the esophago-gastric junction or tumors with esophageal invasion.^{11 12}
21
22 87 A meta-analysis comparing linear anastomosis with circular anastomosis in laparoscopic distal
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24
25 88 gastrectomy (LDG) suggested that linear anastomosis is better than circular anastomosis in LDG¹³.
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27 89 However, considering the differences between TLTG and LDG in terms of surgical methods,
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29
30 90 surgical objects and surgical difficulties, this conclusion cannot be applied to guide the
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33 91 implementation of TLTG.

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36 92 Therefore, the choice of staplers for complete esophagojejunostomy of TLTG is still an unclear
37
38
39 93 and controversial topic.^{7 8 14} Majority of the previous comparisons on contrasting linear and circular
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41 94 stapling anastomosis for esophagojejunostomy in TLTG are retrospective and are based on
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44 95 small-sample studies, further, the results from such investigation have been inconsistent and even
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46 96 contradictory. Therefore, the safety and efficacy of linear stapling anastomosis has not been well
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49 97 resolved in these studies and remains to be confirmed by higher-level evidence. In view of this, a
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52 98 systematic review and meta-analysis will be conducted based on relevant published literature to
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54 99 further explore and compare the safety and efficacy of the linear stapler and circular stapler in TLTG,
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57 100 with the hope of providing a reference to help surgeons choose a suitable stapler.

60 101 **2 Materials and methods**

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4 102 The protocol of the planned systematic review and meta-analysis was prepared in accordance
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6
7 103 with the recommendation from the Preferred Reporting Items for Systematic Review and
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9 104 Meta-Analysis Protocols (PRISMA-P) statement,¹⁵ and this systematic review and meta-analysis will
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12 105 be written in line with PRISMA statement.¹⁶ In addition, this study protocol was registered with the
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14 106 international prospective register of systematic reviews PROSPERO (CRD42018111680).¹⁷
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17 18 107 **2.1 Literature-search strategy**

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21 108 Relevant studies will be searched on PubMed, Cochrane Library, Embase, CNKI, and Wanfang
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24 109 Databases in accordance with the population, intervention, control and outcomes (PICO) criteria
25
26 110 from Jan-1990 to the actual start date. The studies comparing linear stapler with circular stapler for
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29 111 esophagojejunostomy in TLTG will be included. The following MeSH terms and their combinations
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31 112 will be searched in [Title/Abstract]: i) "*linear stapler*" OR "*overlap*" OR "*FEEA*" OR "*T-shaped*" OR
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33
34 113 "*π-shaped*" OR "*delta-shaped*"; ii) "*circular stapler*" OR "*OrVil™*" OR "*hemidouble stapling*
35
36
37 114 *technique*" OR "*double stapling technique*"; iii) "*totally laparoscopic*"; iv) "*total gastrectomy*". The
38
39 115 related-articles function will be used to increase the search scope, and the computer search will be
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42 116 supplemented with manual screening of the reference lists of all retrieved studies, review articles and
43
44 117 conference abstracts.
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47 48 118 **2.2 Inclusion criteria**

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51 119 (1) The subjects were the patients who had undergone esophagojejunostomy in totally
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54 120 laparoscopic total gastrectomy, and preoperative or postoperative histopathologic examination
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56 121 confirmed gastric cancer; (2) According to the different anastomosis methods used for
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59 122 esophagojejunostomy in digestive tract reconstruction, patients were divided into linear stapling
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4 123 anastomosis and circular stapling anastomosis groups; (3) The study types were randomized
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6 124 controlled trials (RCTs), non-RCTs, or observational comparative studies; (4) The original literature
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9 125 should have terms including intraoperative conditions, postoperative specimens, postoperative
10
11
12 126 recovery, postoperative complications, postoperative complications, or have at least one of these
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14 127 research data; (6) Pooled results can be formulated by the statistical index, such as odds ratio (OR),
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16
17 128 relative risk (RR), or weighted mean difference (WMD). (6) For multiple similar studies from the
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19
20 129 same research institution, a recent or higher quality study will be selected.
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23 130 **2.3 Exclusion criteria**

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25
26 131 (1) The literature including cases of open surgery or hand-assisted laparoscopic total
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28
29 132 gastrectomy; (2) The literature that did not respectively provide the data for linear stapler group and
30
31 133 circular stapler group or the surgical method was not clearly stated in the literature; (3) The literature
32
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34 134 was a case report, case series, letters, review, or non-control study without control group; (4) The
35
36 135 sample size was too small, and the number of cases was less than 20 cases; (5) Other treatments were
37
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39 136 differently performed between two groups during pre and post operation, and these treatments
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41
42 137 probably affected the observed outcome in the studies; (6) The literature was a repeated publication.
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45 138 **2.4 Study screening and selection**

46
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48 139 Any duplication will be identified and removed using the EndNote X8 reference management
49
50
51 140 software (Clarivate Analytics, Thomson Place, Boston, USA). Under the pre-established inclusion
52
53 141 and exclusion criteria, the titles and abstracts of all remaining literatures are carefully read and
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56 142 examined to exclude obviously unrelated documents. The full text of the screened literature will be
57
58
59 143 deeply and carefully read to determine whether it is to be included. All steps will be independently
60

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4 144 conducted and cross-checked by three reviewers, and all disagreements will be resolved by
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6
7 145 discussion with the senior authors (Xueqing Yao) until a consensus be reached. The detailed process
8
9 146 of study selection will be displayed in detail in a PRISMA-compliant flow diagram (Figure 1).
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12 147 **2.5 Data extraction and outcomes of interest**

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16 148 Three reviewers will independently extract the data, and any discrepancy will be resolved by
17
18 149 discussion until a consensus is reached. All extracted data will be filled in data extraction sheets
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20
21 150 created by Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington, USA). The main
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24 151 extracted information are as follows: (1) study characteristics (e.g: first author's name, year of
25
26 152 publication, country of study, study design, study period, number of patients, number of patients with
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29 153 linear stapler, number of patients with circular stapler); (2) participant characteristics (e.g: age, sex,
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31 154 ethnicity, body mass index (BMI), cancer stage, American Society of Anesthesiologists (ASA)
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33
34 155 score); (3) primary outcomes: anastomotic leakage, anastomotic stricture, anastomotic hemorrhage,
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37 156 total postoperative complications; (4) secondary outcomes: first exhaust time after operation, first
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39 157 feeding time, total operation time, reconstruction time of digestive tract, estimated blood loss, lymph
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42 158 node harvest, the distance from the proximal margin of the tumor, postoperative hospital stay. Any
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44 159 missing information is supplemented by contacting the original author by telephone or e-mail.
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47 160 **2.6 Quality assessment**

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51 161 The quality of the studies will be independently scored by three reviewers using the Cochrane
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54 162 risk of bias tool or the Newcastle-Ottawa Quality Assessment Scale (NOS).¹⁸ The methodological
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56 163 quality of randomized controlled trials will be assessed using the Cochrane risk of bias tool.¹⁹ The
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59 164 methodological quality of non-random studies such as case-control and cohort studies will be
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4 165 assessed by the NOS, which consists of three factors: patient selection, comparability of the study
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6 166 groups, and assessment of outcome. A score of 0–9 (allocated as stars) will be allocated to each study
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9 167 except for RCTs. RCTs and observational studies achieving six or more stars will be considered to be
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12 168 of high-quality studies. In cases where discrepancies arose, studies will be re-examined and a
13
14 169 consensus will be reached through discussion.
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17 170 **2.7 Statistical analysis**

21 171 All the meta-analyses will be performed using Review Manager 5.3 (Cochrane Collaboration,
22
23
24 172 Oxford, UK). The weighted mean difference (WMD) and odds ratio (OR) will be used to compare
25
26 173 continuous and dichotomous variables respectively, and all the results will be reported with 95%
27
28
29 174 confidence intervals. For the literature reporting median and range of continuous variables, the mean
30
31 175 and standard deviation (SD) will be extracted using the method described by Hozo et al.²⁰
32
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34 176 Continuous variables that only provided quartiles or mean and SD could not be extracted will be
35
36
37 177 eliminated. Assessment of statistical heterogeneity among the studies will be undertaken using the χ^2
38
39 178 and I^2 statistical tests. Where there is no obvious statistical heterogeneity among the studies as
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42 179 denoted by a P value ≥ 0.1 or $I^2 \leq 50\%$, the fixed effect model will be used for meta-analysis.
43
44 180 Conversely, in cases where statistical heterogeneity is observed among studies with a P value < 0.1
45
46
47 181 or $I^2 > 50\%$, a random effect model will be used for meta-analysis. If concerns for high heterogeneity
48
49
50 182 (I^2 value $> 75\%$ indicates high heterogeneity)²¹ exist, a sensitivity analysis will be performed.
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53 183 **2.8 Assessment of publication bias**

56 184 The potential publication bias will be investigated using funnel plots drawn by the STATA SE
57
58
59 185 version 12.0 software. The publication bias will be assessed by visual inspection of the Begg's funnel
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4 186 plots, whereby, if the standard error of logOR of each study is plotted against its logOR, an
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6 187 asymmetric plot suggests a possible publication bias.²² In addition, the asymmetry of the funnel-plot
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9 188 will be assessed using the Egger linear regression test at the $p < 0.10$ significance level.²³
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12 189 **2.9 Subgroups analysis**

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16 190 To explore the potential heterogeneity, subgroup meta-analyses will be performed based on
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18 191 different characteristics of the patient (e.g: age, sex, ethnicity, BMI, cancer stage) as well as by study
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21 192 characteristics (e.g: country of study, study design, year of publication, study period, number of
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24 193 patients).

25 26 27 194 **2.10 Sensitivity analysis**

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30 195 In order to ensure the robustness and reliability of evidence, sensitivity analysis will be
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33 196 performed to assess the effect of studies with a high risk of bias. The results will be compared to
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35 197 decide whether low-quality studies should be excluded based on sample size and quality assessment
36
37
38 198 of studies or effect on pooled effective size. In addition, a leave-one-out sensitivity meta-analysis
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41 199 might be considered if a study involving a large number of patients was based on different types of
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43 200 studies.²⁴
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46 201 **2.11 Patient and public involvement**

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50 202 Not applicable. Patient and public involvement will not be required because this proposed
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52 203 systematic review and meta-analysis is based on previously published data, which does not include
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54
55 204 intervention data on patients.

56 57 205 **3 Discussion**

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4 206 Recent decades have witnessed significant advancements in the skills-set and the equipment for
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6
7 207 laparoscopic surgery advance. This has not only expanded the application scope of laparoscopic
8
9 208 surgery in gastric cancer,^{25 26} but has also lead to the transition of laparoscopic reconstruction of the
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12 209 digestive tract in gastric cancer from laparoscopic-assisted surgery to totally laparoscopic surgery.⁶
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14 210 However, the application of TLTG for total laparoscopic digestive tract reconstruction faces some
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17 211 difficulties due to its high technical requirements.^{14 27} However, total laparoscopic digestive tract
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20 212 reconstruction after TLTG has obvious theoretical advantages.^{28 29} For instance, the
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22 213 pneumoperitoneum provides a larger operation space for surgery and the multi-angle lens provides
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25 214 direct vision for operation to avoid damage. Therefore, TLTG is a promising technique for gastric
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27 215 cancer.

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31 216 It is no doubt that the development of stapler technology has promoted the development of
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33 217 laparoscopic gastrointestinal operation, especially in TLTG. Presently, mechanical anastomosis for
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36 218 esophagojejunostomy in TLTG is mainly divided into two types: end-to-side anastomosis using the
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38
39 219 circular stapler and side-to-side/functional end-to-end anastomosis using the linear stapler.⁶⁻⁸
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41
42 220 The circular stapling anastomosis method is divided into different methods according to the
43
44 221 placement of the nail anvil: the traditional method of direct insertion, reverse anvil method and
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46
47 222 OrVilTM method.³⁰⁻³² However, in the first two methods, the main body of the stapler cannot enter the
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49
50 223 abdominal cavity through the trocar, which requires that the pneumoperitoneum be closed and a
51
52 224 small auxiliary incision is often created, thereby reducing the fluency and efficiency of the operation.
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55 225 In addition, the difficult in operation of the esophageal purse suture and the placement of the nail
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57 226 anvil also limits the application of these two methods. Although the OrVilTM method does not require
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60 227 the placement of an anvil through the abdominal cavity, it requires the services of an anesthesiologist

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4 228 and a special anvil placement device.⁹ The price of the special device is high, and the extraction of
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6 229 the guide tube might cause intra-abdominal infection.^{9 27 33}
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10 230 Linear stapling anastomosis involves functional end-to-end anastomosis (FEEA method) as well
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12 231 as side-to-side anastomosis (Overlap method).³⁴ This technique is appropriate for total laparoscopic
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15 232 gastrectomy compared to using circular stapling anastomosis.^{11 29 33} Based on the published
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18 233 literatures and the experience of our center, the linear stapler has the following advantages^{28 35 36}: (1)
19
20 234 linear stapler can be easily put into the abdominal cavity via a trocar and has a better visual field; (2)
21
22
23 235 the operation of linear stapler is simple and convenient, and the requirement for the surgeon is lower
24
25 236 compared to using a circular stapler; (3) the circular stapler with two rows of staples, but the linear
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27
28 237 stapler provides three rows of nail technology to theoretically improve the safety of the anastomosis.
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31 238 However, although some advantages have been reported for linear stapler, its application in
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33 239 laparoscopic total gastrectomy has some limitations such as^{8 14}: (1) a longer stump of the esophagus
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36 240 is required which limits the incisal margin; (2) when the anastomosis plane is higher than the plane
37
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39 241 of esophageal hiatus, the operation is performed in a narrow thoracic cavity and the visual field is
40
41 242 narrowed; (3) the pulling and folding of the jejunum arm might increase the tension in the
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44 243 anastomosis. Whether the possibly increased tension could increase the risk of anastomotic leak is an
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46 244 important topic needed to be resolved in this study. The discussed anastomotic methods have their
47
48
49 245 advantages and disadvantages in the anastomosis of the esophagus between jejunum, and it is not
50
51
52 246 clear which anastomosis technique is superior.¹⁴ Further, no standard methods have been established
53
54 247 to guide the selection.^{37 38} Therefore, it is meaningful and necessary to conduct a systematic review
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57 248 and meta-analysis to provide a reference that could aid clinical surgeons in choosing
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59 249 a more appropriate alternative for their patients.
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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

For peer review only

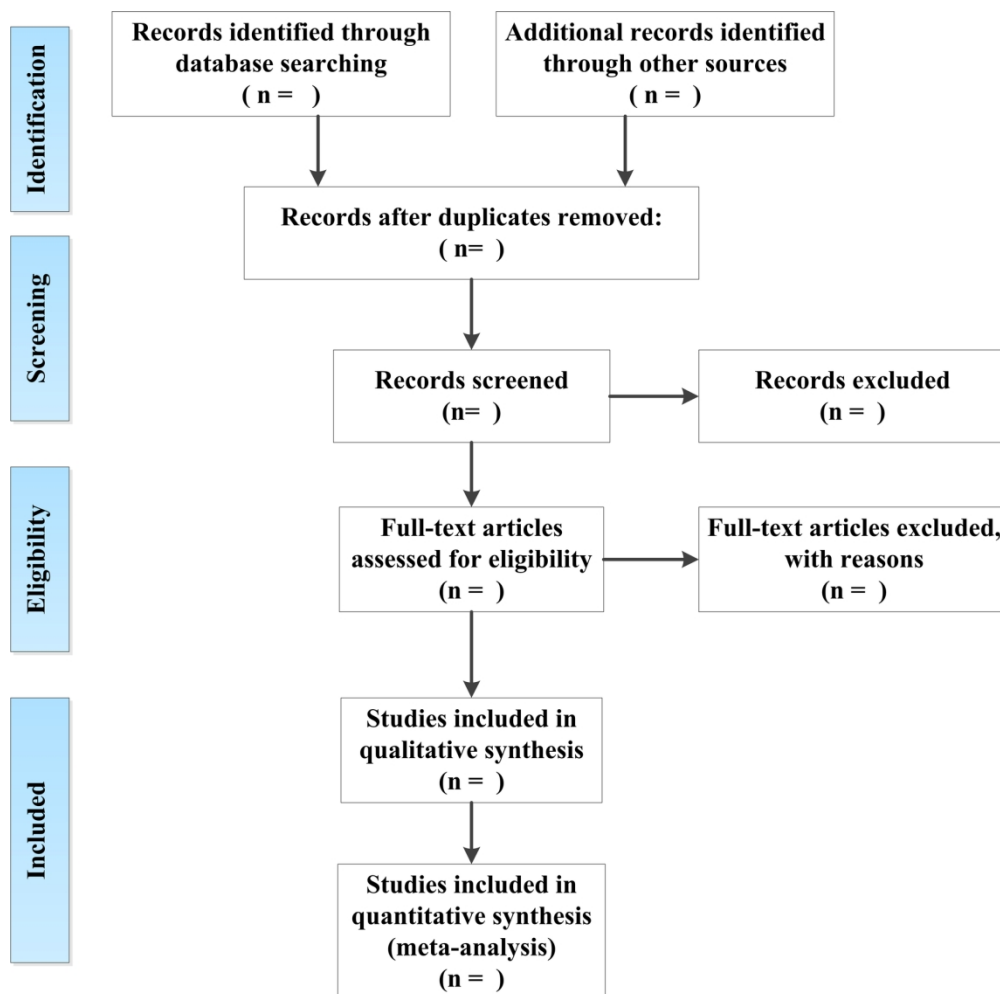


Figure 1 Flow diagram of study selection

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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	None
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	45
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	5-17
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input type="checkbox"/>	<input checked="" type="checkbox"/>	None
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	272
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	273-278
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	<input checked="" type="checkbox"/>	None
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	58
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	107
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	111-114
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input type="checkbox"/>	<input checked="" type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	160; 183
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input type="checkbox"/>	<input checked="" type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	170
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	189; 194
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>	<input checked="" type="checkbox"/>	None
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	183
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-028216.R2
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Date Submitted by the Author:	04-Apr-2019
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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Gastroenterology and hepatology, Oncology, Surgery
Keywords:	linear stapler, circular stapler, totally laparoscopic total gastrectomy, esophagojejunostomy

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Manuscripts

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4 1 **Comparison of the safety and efficacy between linear stapler and circular stapler in totally**
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9 3 **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

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4 42 review and meta-analysis is based on previously published data, which does not include intervention
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12 45 **PROSPERO registration number:** CRD42018111680.

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15 46 **Keywords:** linear stapler; circular stapler; totally laparoscopic total gastrectomy;
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19 20 21 48 **Strengths and limitations of this study**

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26 50 compare the safety and efficacy of the linear stapler and circular staplers in TLTG.

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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 OrVilTM does not pass through the abdominal cavity, a top-down placement method is required, but the operation

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4 80 requires an anesthesiologist to cooperate.⁹ Compared with the circular stapler, linear stapler has some
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6 81 advantages in esophagojejunostomy.¹⁰ For example, it can easily enter the abdominal cavity through
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12 83 disadvantage of linear anastomosis is the need for a long-enough esophageal stump for anastomosis,
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22 87 A meta-analysis comparing linear anastomosis with circular anastomosis in laparoscopic distal
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25 88 gastrectomy (LDG) suggested that linear anastomosis is better than circular anastomosis in LDG¹³.
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27 89 However, considering the differences between TLTG and LDG in terms of surgical methods,
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36 92 Therefore, the choice of staplers for complete esophagojejunostomy of TLTG is still an unclear
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57 100 with the hope of providing a reference to help surgeons choose a suitable stapler.

60 101 **2 Materials and methods**

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14 106 international prospective register of systematic reviews PROSPERO (CRD42018111680).¹⁷
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17 18 107 **2.1 Literature-search strategy**

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24 109 Databases in accordance with the population, intervention, control and outcomes (PICO) criteria
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26 110 from Jan-1990 to Jul-2019. The studies comparing linear stapler with circular stapler for
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29 111 esophagojejunostomy in TLTG will be included. The following MeSH terms and their combinations
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31 112 will be searched in [Title/Abstract]: i) "*linear stapler*" OR "*overlap*" OR "*FEEA*" OR "*functional*
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34 113 *end-to-end anastomosis*" OR "*T-shaped*" OR "*π-shaped*" OR "*delta-shaped*"; ii) "*circular stapler*"
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37 114 OR "*OrVil™*" OR "*hemidouble stapling technique*" OR "*double stapling technique*"; iii) "*totally*
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39 115 *laparoscopic*"; iiiii) "*total gastrectomy*". The related-articles function will be used to increase the
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44 117 lists of all retrieved studies, review articles and conference abstracts.
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47 48 118 **2.2 Inclusion criteria**

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51 119 (1) The subjects were the patients who had undergone esophagojejunostomy in totally
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54 120 laparoscopic total gastrectomy, and preoperative or postoperative histopathologic examination
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56 121 confirmed gastric cancer; (2) According to the different anastomosis methods used for
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4 123 anastomosis and circular stapling anastomosis groups; (3) The study types were randomized
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6 124 controlled trials (RCTs), non-RCTs, or observational comparative studies; (4) The original literature
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9 125 should have terms including intraoperative conditions, postoperative specimens, postoperative
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14 127 research data; (6) Pooled results can be formulated by the statistical index, such as odds ratio (OR),
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17 128 relative risk (RR), or weighted mean difference (WMD). (6) For multiple similar studies from the
18
19
20 129 same research institution, a recent or higher quality study will be selected.
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23 130 **2.3 Exclusion criteria**

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26 131 (1) The literature including cases of open surgery or hand-assisted laparoscopic total
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29 132 gastrectomy; (2) The literature that did not respectively provide the data for linear stapler group and
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31 133 circular stapler group or the surgical method was not clearly stated in the literature; (3) The literature
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34 134 was a case report, case series, letters, review, or non-control study without control group; (4) The
35
36 135 sample size was too small, and the number of cases was less than 20 cases. The studies with fewer
37
38
39 136 than 20 cases are usually considered small-sample studies and were excluded by authors in some
40
41
42 137 published meta-analysis articles.¹⁸ (5) Other treatments were differently performed between two
43
44 138 groups during pre and post operation, and these treatments probably affected the observed
45
46
47 139 outcome in the studies; (6) The literature was a repeated publication.
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50 140 **2.4 Study screening and selection**

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53 141 Any duplication will be identified and removed using the EndNote X8 reference management
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56 142 software (Clarivate Analytics, Thomson Place, Boston, USA). Under the pre-established inclusion
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58
59 143 and exclusion criteria, the titles and abstracts of all remaining literatures are carefully read and
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4 144 examined to exclude obviously unrelated documents. The full text of the screened literature will be
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6
7 145 deeply and carefully read to determine whether it is to be included. All steps will be independently
8
9 146 conducted and cross-checked by three reviewers, and all disagreements will be resolved by
10
11
12 147 discussion with the senior authors (Xueqing Yao) until a consensus be reached. The detailed process
13
14 148 of study selection will be displayed in detail in a PRISMA-compliant flow diagram (Figure 1).

17 18 149 **2.5 Data extraction and outcomes of interest**

19
20
21 150 Three reviewers will independently extract the data, and any discrepancy will be resolved by
22
23
24 151 discussion until a consensus is reached. All extracted data will be filled in data extraction sheets
25
26 152 created by Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington, USA). The main
27
28
29 153 extracted information are as follows: (1) study characteristics (e.g: first author's name, year of
30
31 154 publication, country of study, study design, study period, number of patients, number of patients with
32
33
34 155 linear stapler, number of patients with circular stapler); (2) participant characteristics (e.g: age, sex,
35
36
37 156 ethnicity, body mass index (BMI), cancer stage, American Society of Anesthesiologists (ASA)
38
39 157 score); (3) primary outcomes: anastomotic leakage, anastomotic stricture, anastomotic hemorrhage,
40
41
42 158 total postoperative complications; (4) secondary outcomes: time to first instance of passing gas after
43
44
45 159 surgery, first feeding time, total operation time, reconstruction time of digestive tract, estimated
46
47 160 blood loss, lymph node harvest, the distance from the proximal margin of the tumor, postoperative
48
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50 161 hospital stay. Any missing information is supplemented by contacting the original author by
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52 162 telephone or e-mail.

55 163 **2.6 Quality assessment**

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59 164 The quality of the studies will be independently scored by three reviewers using the Cochrane
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4 165 risk of bias tool or the Newcastle-Ottawa Quality Assessment Scale (NOS).¹⁹ The methodological
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7 166 quality of randomized controlled trials will be assessed using the Cochrane risk of bias tool.²⁰ The
8
9 167 methodological quality of non-random studies such as case-control and cohort studies will be
10
11
12 168 assessed by the NOS, which consists of three factors: patient selection, comparability of the study
13
14 169 groups, and assessment of outcome. A score of 0–9 (allocated as stars) will be allocated to each study
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16
17 170 except for RCTs. RCTs and observational studies achieving six or more stars will be considered to be
18
19
20 171 of high-quality studies. In cases where discrepancies arose, studies will be re-examined and a
21
22 172 consensus will be reached through discussion.

25 173 **2.7 Statistical analysis**

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29 174 All the meta-analyses will be performed using Review Manager 5.3 (Cochrane Collaboration,
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31 175 Oxford, UK). The weighted mean difference (WMD) and odds ratio (OR) will be used to compare
32
33
34 176 continuous and dichotomous variables respectively, and all the results will be reported with 95%
35
36
37 177 confidence intervals. For the literature reporting median and range of continuous variables, the mean
38
39 178 and standard deviation (SD) will be extracted using the method described by Hozo et al.²¹
40
41
42 179 Continuous variables that only provided quartiles or mean and SD could not be extracted will be
43
44 180 eliminated. Assessment of statistical heterogeneity among the studies will be undertaken using the χ^2
45
46
47 181 and I^2 statistical tests. Where there is no obvious statistical heterogeneity among the studies as
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50 182 denoted by a P value ≥ 0.1 or $I^2 \leq 50\%$, the fixed effect model will be used for meta-analysis.
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52 183 Conversely, in cases where statistical heterogeneity is observed among studies with a P value < 0.1
53
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55 184 or $I^2 > 50\%$, a random effect model will be used for meta-analysis. If concerns for high heterogeneity
56
57 185 (I^2 value $> 75\%$ indicates high heterogeneity)²² exist, a sensitivity analysis will be performed.
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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

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

2.12 Ethics and dissemination

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

3 Discussion

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

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

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4 228 The circular stapling anastomosis method is divided into different methods according to the
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7 229 placement of the nail anvil: the traditional method of direct insertion, reverse anvil method and
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9 230 OrVil™ method.³¹⁻³³ However, in the first two methods, the main body of the stapler cannot enter the
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12 231 abdominal cavity through the trocar, which requires that the pneumoperitoneum be closed and a
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15 232 small auxiliary incision is often created, thereby reducing the fluency and efficiency of the operation.
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17 233 In addition, the difficult in operation of the esophageal purse suture and the placement of the nail
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20 234 anvil also limits the application of these two methods. Although the OrVil™ method does not require
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22 235 the placement of an anvil through the abdominal cavity, it requires the services of an anesthesiologist
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25 236 and a special anvil placement device.⁹ The price of the special device is high, and the extraction of
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27 237 the guide tube might cause intra-abdominal infection.^{9 28 34}

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31 238 Linear stapling anastomosis involves functional end-to-end anastomosis (FEEA method) as well
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33 239 as side-to-side anastomosis (Overlap method).³⁵ This technique is appropriate for total laparoscopic
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36 240 gastrectomy compared to using circular stapling anastomosis.^{11 30 34} Based on the published
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39 241 literatures and the experience of our center, the linear stapler has the following advantages^{29 36 37}: (1)
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41 242 linear stapler can be easily put into the abdominal cavity via a trocar and has a better visual field; (2)
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43
44 243 the operation of linear stapler is simple and convenient, and the requirement for the surgeon is lower
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46 244 compared to using a circular stapler; (3) the circular stapler with two rows of staples, but the linear
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49 245 stapler provides three rows of nail technology to theoretically improve the safety of the anastomosis.
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52 246 However, although some advantages have been reported for linear stapler, its application in
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54 247 laparoscopic total gastrectomy has some limitations such as ^{8 14}: (1) a longer stump of the esophagus
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57 248 is required which limits the incisal margin; (2) when the anastomosis plane is higher than the plane
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59 249 of esophageal hiatus, the operation is performed in a narrow thoracic cavity and the visual field is
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4 250 narrowed; (3) the pulling and folding of the jejunum arm might increase the tension in the
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7 251 anastomosis. Whether the possibly increased tension could increase the risk of anastomotic leak is an
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9 252 important topic needed to be resolved in this study. The discussed anastomotic methods have their
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12 253 advantages and disadvantages in the anastomosis of the esophagus between jejunum, and it is not
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15 254 clear which anastomosis technique is superior.¹⁴ Further, no standard methods have been established
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17 255 to guide the selection.^{38 39} Therefore, it is meaningful and necessary to conduct a systematic review
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20 256 and meta-analysis to provide a reference that could aid clinical surgeons in choosing
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22 257 a more appropriate alternative for their patients.

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26 258 In this review, in order to collect all existing and available literature, RCTs and non-RCTs as
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28 259 well as observational studies will be included. Because of the novelty of this research topic, a few
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31 260 studies had been reported. However, the non-RCTs and observational studies might affect the quality
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33 261 of the evidence and lower the confidence level of the result. Besides, there are many factors such as
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36 262 different standards of choosing patients, different proficiency in laparoscopic techniques and
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39 263 different habits or methods of using the stapler by different surgeons in different regions, which
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41 264 might influence the results. Hence, in view of these, it is very important for this review to perform
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44 265 subgroup analysis and sensitivity analysis. Further analysis and explanations will be carried out in
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46 266 our review to ensure the robustness and reliability of the results.

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50 267 In summary, this systematic review and meta-analysis will help to determine the differences in
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52 268 terms of safety and efficacy between linear stapler and circular stapler in TLTG. Furthermore, the
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55 269 findings of this study will not only help the surgeons in choosing the surgical methods, but also
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57 270 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

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

294 current version of manuscript: Tianyou Liao, Leilei Deng, Xueqing Yao, Manzhao Ouyang.

295 Ethics approval and consent to participate

296 Not applicable

297 Consent for publication

298 Not applicable

299 Competing interests

300 The authors declare that they have no competing interests.

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3 the esophagus and jejunum using EEA OrVil in laparoscopic total gastrectomy and proximal gastrectomy. *Surg*
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Figure 1 Flow diagram of study selection

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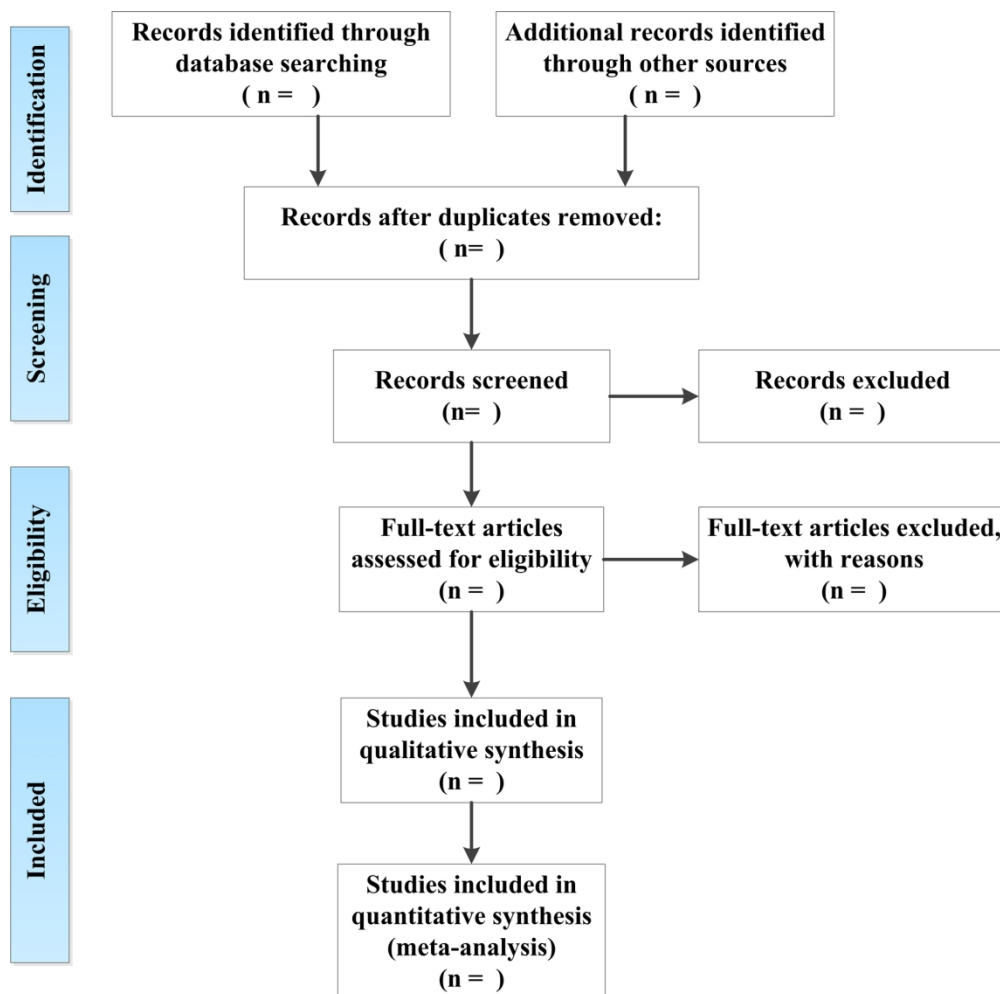


Figure 1 Flow diagram of study selection

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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" type="checkbox"/>	None
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	43
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	5-17
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input type="checkbox"/>	<input checked="" type="checkbox"/>	None
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	278
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	279-284
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	<input checked="" type="checkbox"/>	None
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	56
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	105
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	109-113
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input type="checkbox"/>	<input checked="" type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	161; 184
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input type="checkbox"/>	<input checked="" type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	171
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	190; 195
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>	<input checked="" type="checkbox"/>	None
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	184
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	None