Effectiveness of additional antireflux surgery after resection of oesophagogastric junction cancer: protocol for a systematic review and meta-analysis

Na Wang, Peng Zheng, Yang Yu, Lei Gao, Yu Li, Fanghui Ding, Bofang Wang, Hao Chen

INTRODUCTION

Oesophageal and gastric cancers are two common types of digestive system malignant tumours with high incidence and mortality.\(^1\)\(^2\)

In the past year, approximately 1033 701 new cases of gastric cancer and 572 034 new cases of oesophageal cancer have been diagnosed globally, and resulted in 782 685 and 508 585 deaths, respectively.\(^1\) The incidence rates varied across regions depending on the degree of economic development and associated social and lifestyle factors.

Oesophagogastric junction (OGJ) cancer, a tumour with characteristic occurrence and location, is associated with various treatment challenges, and hence, requires further research. Surgery remains the best option for tumours detected in the early phases. Surgical treatment for OGJ cancer includes resection of the primary tumour, lymphadenectomy and reconstruction of the digestive tract. However, during radical surgery, damage to the natural antireflux mechanisms between the stomach and oesophagus is unavoidable; therefore, the surgery is associated with high incidence of postoperative gastro-oesophageal reflux in patients with OGJ cancer. Reflux causes acid regurgitation, belching, retrosternal pain and reflux oesophagitis, which significantly influence patients’ quality of life.\(^3\)\(^4\) Aimed at preventing postoperative reflux, researchers have developed antireflux strategies, which include additional pyloroplasty or fundoplication after radical cancer surgery.\(^5\)\(^-\)\(^7\) Fundoplication is a surgical method previously used

ABSTRACT

Introduction Gastro-oesophageal reflux is common in patients with oesophagogastric junction (OGJ) cancer following radical surgery. We aim to conduct a systematic review to investigate the effectiveness and clinical value of additional antireflux surgery (pyloroplasty and fundoplication) for OGJ cancer.

Methods and analysis We intend to search Medline, Cochrane Library and Embase databases for studies published in English, from database inception to October 2022. Randomised controlled trials and (non-random) controlled clinical trials will be eligible for inclusion. We will search for all eligible studies that have compared proximal gastrectomy plus additional antireflux surgery and proximal gastrectomy alone in patients with resectable OGJ cancer. All potential outcomes related to gastro-oesophageal reflux, including occurrence of reflux symptoms, reflux oesophagitis, reflux occurrence based on barium meal examination, pH of fluid from the lower oesophagus, and 24-hour oesophageal pH test will be assessed as the primary outcomes. Other outcomes, such as patients’ survival and postoperative complications (eg, stenosis, infection and leak) will also be analysed. Two reviewers will independently screen the literature, extract data and assess the risk of bias in the included studies; subsequently, a meta-analysis will be performed using RevMan V.5.3 software to pool the results. The χ\(^2\) and I\(^2\) tests will be used for heterogeneity assessment and sources of heterogeneity will be explored using subgroup analysis. The Grading of Recommendations, Assessment, Development and Evaluation method will be applied to assess the level of evidence.

Ethics and dissemination This proposed study is a secondary analysis of previously published data. Therefore, ethics approval is not required. The results will be presented for publication in a peer-reviewed journal and data will be stored in public databases.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The planned search is extensive, and the research question will be evaluated comprehensively.
⇒ The presence of heterogeneity across the included studies may impact the reliability of the meta-analysis.
⇒ The language is limited to English.

for treating gastro-oesophageal reflux disease; however, some researchers have adapted it specifically for antireflux prevention in OGJ cancer. Presently, many surgeons are attempting these antireflux surgeries. However, the antireflux effects of these additional surgeries remain unclear in patients who undergo radical resection of OGJ cancer.

Therefore, to address the clinical question, we plan to conduct a systematic review and meta-analysis of studies that have assessed the effectiveness and safety of antireflux surgeries in patients with OGJ cancer.

Objectives
This study will evaluate all trials comparing the outcomes between radical surgery and radical surgery combined with additional antireflux surgery, aim to investigate the effects and clinical value of additional antireflux surgery for OGJ cancer, and provide a reference for surgeons in clinical practice.

METHODS AND ANALYSIS
Participants
We will include patients with adenocarcinoma of the oesophagogastric junction (AOG), who were diagnosed pathologically, have no adjacent tissue or organ invasion and distant metastases, and are suitable for radical resection. AOG is defined as ‘a cancer with the center located within 5 cm proximal and distal to the anatomical OGJ as well as infiltrating the OGJ’, according to the Siewert classification, which includes the Siewert I, II and III subtypes. There will be no restrictions regarding patients’ age, sex, race and place of residence.

Interventions and controls
Patients in the intervention group would have undergone proximal gastrectomy plus additional antireflux surgery. Intraoperatively, complete lymph node dissection and gastro-oesophageal anastomosis would have been completed as per the standard method. Open and laparoscopic surgeries will be eligible. Additional antireflux surgery refers to an additional surgery after radical surgery, to reduce the occurrence of postoperative reflux symptoms; specifically, fundoplication or pyloroplasty. Patients whose surgeries were combined with other antireflux strategies will be excluded. In the control group, radical surgery would have been performed without additional antireflux surgery.

Outcomes
All potential outcomes related to gastro-oesophageal reflux, including occurrence of reflux symptoms, reflux oesophagitis, reflux occurrence based on barium meal examination, pH of fluid from the lower oesophagus and 24-hour oesophageal pH test will be assessed as the primary outcomes. Other outcomes, such as patients’ survival and postoperative complications (eg, stenosis, infection and leak) will also be analysed.

Studies
All relevant randomised controlled trials or controlled clinical trials (with non-random methods of allocating participants to a treatment, for example, date of birth, hospital record number or alternation) published in English will be considered.

Information sources
We will search the Medline, Cochrane Library and Embase databases for studies published from their inception to October 2022. Additionally, we will perform a manual search in relevant professional journals and review the references of studies included in published systematic reviews or meta-analyses with a similar topic, to retrieve additional studies.

Search strategy
A combination of subject and free-text terms will be used to conduct the searches. We will use the terms ‘neoplasms’, ‘cancer’, ‘esophagogastric junction’, ‘gastro-oesophageal junction’ ‘cardia’, ‘esophagogastrostomy’, ‘surgery’ and ‘randomised controlled trial’ in global databases. The full search strategy is presented in the online supplemental material.

Data management
All study records will be processed using EndNote X9, which can identify and remove duplicates. All extracted data will be stored in a Microsoft Excel spreadsheet.

Study selection and data collection process
Based on the aim of this review and established inclusion criteria, two researchers will independently screen titles and abstracts identified in the initial search and will review the full texts of the selected studies. Disagreements will be resolved through in-person discussion, or consultation with a third researcher, if necessary.

Data Items
A predeveloped information extraction table will be used to extract relevant information in the included studies. This will include bibliographic information (ie, study title, author name(s) and year of publication), general characteristics of participants (ie, sample size, mean age, sex ratio, pathological type and type of radical surgery), intervention details (ie, antireflux surgery) and outcomes with data.

Risk of bias in individual studies
Two reviewers will independently assess the risk of bias in each included trial using the Cochrane Collaboration’s tool for assessing the risk of bias. Disagreements will be resolved by discussion between the two reviewers. If a consensus cannot be reached, a third reviewer will be employed as an arbiter. The main criteria for measuring the risk of bias will include the following: random sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; completeness of outcome data; and selective reporting and other sources.
of bias (baseline imbalance and source of funding). The risk of bias for each criterion will be judged using the following standards: yes (low risk of bias), no (high risk of bias) or unclear (either lack of information or uncertainty over the potential for bias).

**Data synthesis**

All statistical tests will be calculated using RevMan V.5.3, and findings will be presented using 95% CIs. We will use the OR as a statistical index for dichotomous data. For continuous outcomes, the mean difference will be calculated by weighing the absolute change based on group size in cases where the trials employ comparable scales; however, if different scales are used to measure the same conceptual domain, we will calculate the standardised mean differences. Survival data will be pooled using HRs to estimate the difference in survival between the groups. Before data analysis, we will assess heterogeneity using $\chi^2$ and I² tests. Additionally, sources of heterogeneity will be explored using subgroup analyses, according to the types of antireflux surgeries, pathological type and study designs. To determine the robustness of the observed results, a sensitivity analysis will be performed by removing low-quality studies, and a random-effects model will be applied if they are determined to be heterogeneous ($\chi^2$ p<0.05, I²≥50%). Alternately, a fixed-effects model will be used. Results will be illustrated using forest plots, and pooled estimates will be reported. A value of p<0.05 will be considered statistically significant.

**Meta-biases**

We will explore reporting bias graphically using a funnel plot, and statistically using Egger’s test, if 10 or more studies are available.10 A value of p<0.05 will be used to indicate publication bias.

**Confidence in cumulative evidence**

The Grading of Recommendations, Assessment, Development and Evaluation method will be applied to assess the level of evidence obtained from this systematic review.11

**Patient and public involvement**

None.

**ETHICS AND DISSEMINATION**

This study is a systematic review and meta-analysis, which is a secondary analysis of published data. Therefore, ethics approval is not required. The results will be presented for publication in a peer-reviewed journal and commutation in academic conference. Data generated during this study will be stored in public databases and will be accessible on reasonable request.

**DISCUSSION**

Gastro-oesophageal reflux is one of the most common postoperative complications in patients with OGJ cancer. Its incidence after radical resection is reported to reach 90%,12 which significantly decreases the patients’ quality of life. Clinically, antireflux strategies have been designed to include an antireflux operation to the radical resection.13 However, the significance of these additional antireflux surgeries is unclear. Surgical difficulties and risks increase with the combination of such procedures; therefore, it is necessary to determine whether these additional antireflux surgeries can improve outcomes in patients with OGJ cancer after radical resection, and the extent of the benefits. To address this, we propose to conduct a systematic review and meta-analysis, where we will systematically review current studies related to this topic and generate an evidence map with detailed information. The results from our study will guide surgeons in planning surgical strategies.

Our review may have some limitations. First, heterogeneity may exist across all included studies, and may impact the reliability of meta-analysis. To address this, we will explore the sources of heterogeneity using subgroup analyses and adjust our modelling methods for meta-analysis, if necessary. Second, the language is limited to English. Studies published in other languages will not be included in our analysis. This may cause publication bias. Third, there are no strict criteria and definitions for the specific procedures of antireflux surgeries. The representation and application of our results may be challenged in the real world. Therefore, caution will be required when applying our results to antireflux surgeries with patient-personalised adjustments. However, we will present each aspect of our study, and the publication of this protocol will strengthen its transparency and reliability.

**Contributors**

HC and YY conceptualised this manuscript. HC and NW designed the methods for conducting this study. PZ and NW wrote the protocol. NW and LG designed the search strategy and performed preliminary searches. PZ, NW, YY, BW, YL, FD and LD provided guidance for the statistical analysis of the data. All authors suggested improvements for the protocol and approved the final draft of the manuscript. All authors have completed the ICMJE uniform disclosure form (available at...).

**Funding**

This study was supported by the National Natural Science Foundation of China (No. 82160129), Key Talents Project of Gansu Province (No. 2019RCX020), Key Project of Science and Technology in Gansu province (19RZD2WA001), Science and Technology Project of Chengguan District of Lanzhou City (2019CCX0034), Science and Technology Project of Chengguan District of Lanzhou City (2020SHF0039), Science and Technology Project of Chengguan District of Lanzhou City (2020JSCX0073), and Cuiying Scientific and Technological Innovation Program of Lanzhou University Second Hospital (No. CY2017-ZD01). The funders had no roles in the study design, data collection and analysis, decision to publish, or manuscript preparation.

**Competing interests**

None declared.

**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication**

Not applicable.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Supplemental material**

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ORCID iDs
Na Wang http://orcid.org/0000-0002-4589-3717
Yang Yu http://orcid.org/0000-0002-2409-3681
Hao Chen http://orcid.org/0000-0001-9741-9403

REFERENCES