Impact of surgical margin status on the survival outcome after surgical resection of gastric cancer: a protocol for systematic review and meta-analysis

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INTRODUCTION

Gastric cancer is the fifth most frequently diagnosed cancer and the third leading cause of death from cancer in the world.1 Although adjuvant therapies can improve outcomes of some patients, surgical resection is considered to be the first line and only possible radical treatment for gastric cancer.2–4 Complete resection with cancer cell negative (R0) margin has been accepted as the most effective treatment based on the surgical philosophy and even minimal remaining cancer cells will develop recurrences.5–6 The recently reported rate of
positive resection, which included both positive resection (R1) margin (cancer cells presented at the resection margin by pathological examination) and R2 margin (tumour tissue seen at the resection margin on gross examination by the naked eye) was 24.2%. Although the influence of R1 margin on gastric cancer survival has been the topics of many studies, inconsistent conclusions have been reached.\textsuperscript{5,8–18} For example, Kim \textit{et al}.\textsuperscript{17} and Postlewait \textit{et al}.\textsuperscript{14} found that R1 margin was not independently associated with survival while Woo \textit{et al}.\textsuperscript{15} and Nagata \textit{et al}.\textsuperscript{5} revealed R1 margin boded ill for survival. Bickenbach \textit{et al}.\textsuperscript{11} found that R1 margin was an independent predictor of worse survival, but not in patients with >3 positive nodes or T3–4 disease. Schoenfeld \textit{et al}.\textsuperscript{18} found R1 margins were associated with disease-free survival (DFS) but not overall survival (OS).

Raziee \textit{et al}.\textsuperscript{19} conducted a systematic review in 2012 examining R1 and R2 margins of gastric cancer by exploring their predictive factors, impact on survival and optimal strategies for reresection, but it did not perform meta-analysis. It was still uncertain whether R1 margin had negative influence on survival and whether it is worth performing reresection to eliminate R1 margin. Therefore, we plan to conduct a systematic review and meta-analysis to quantitatively explore the impact of R1 margin on gastric cancer survival after curative intent resection. Since the preformal study literature search found that original studies on this topic were almost non-randomised studies (NRS), our systematic review will consider both randomised controlled trials (RCTs) and NRS. The protocol for our research is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA- P),\textsuperscript{20,21} its PRISMA- P checklist file is attached in online supplemental file 1. The findings of the review will be sought published in a peer-reviewed journal, also in the event of insignificant results or null results, and thereby it will be disseminated to clinicians and public available.

OBJECTIVES

The aim of this systematic review and meta-analysis is to explore the following:

1. Whether R1 margin negatively influences the survival of gastric cancer after curative intent resection.
2. Which subgroups are most impacted by R1 margin and which are not?

The study will be conducted based on the following requirements.

Population

Patients who have undergone curative intent resection for gastric cancer diagnosed by pathological examination will be included.

Gastric cancer patients underwent palliative intent resection will be excluded.

Exposure

The exposure will be postoperative R1 margin, which means that cancer cells are identified by pathological examination at the linear, circular, proximal or distal resection margin.

Margin status identified as R1 by intraoperative frozen section but R0 by pathological examination and R2 margin will be excluded.

Control

R0 margin is confirmed by pathological examination.

Outcomes

Primary outcome: time-to-event OS and time-to-event DFS or relevant data to estimate them.

Secondary outcome: 5-year OS rate and 5-year DFS rate or relevant data to estimate them.

Studies in which relevant data about these outcomes are impossible to extract will be excluded.

METHODS

This systematic review and meta-analysis will be conducted according to the PRISMA guidelines.\textsuperscript{22}

Criteria for considering studies

Inclusion criteria

1. RCTs, cohort studies or case–control studies estimating the impact of margin status on gastric cancer survival after curative intent resection.
2. Studies with a minimum of 60 months follow-up reporting time-to-event OS or DFS or reporting 5-year OS rate or 5-year DFS rate.
3. Studies including only human participants.
4. There will be no restrictions on language and publication year.

Exclusion criteria

1. Studies with overlapping data.
2. Studies researching endoscopic submucosal dissection and endoscopic mucosal resection of gastric cancer.

Search strategy

The search strategy will be conducted in two stages.

Bibliographic database searches

A systematic search of PubMed, Embase and the Cochrane Central Register of Controlled Trials databases will be performed from their inceptions to 30 April 2020 to identify all relevant studies. The details of PubMed database search strategy and syntax are shown in table 1.

Searching for other sources

We will manually search the references of relevant articles to further identify eligible studies, and their full texts will be retrieved.

Study selection and data extraction

Records identified according to search strategy will be collated and exported to EndNote VX8 software. Two
reviewers (ZJ and ZC) will independently screen their titles and abstracts. Subsequently, the two independent reviewers will reassess the full texts of the identified studies, verifying the reasons for inclusion and exclusion. Disagreements will be resolved by team consensus.

Data extraction for included studies will be conducted by two reviewers (ZJ and either ZC or YY) independently using a standardised electronic data extraction form (listed in table 2). This form was piloted by all reviewers. The following data will be extracted from all the included studies: first author, publication year, study design, study period, country(region), male rate, age (mean or median), follow-up (mean or median), sample size, R1 margin rate, R0 margin rate, tumour size, tumour site, tumour stage, histologic grade, type of surgery, lymphadenectomy, neoadjuvant or adjuvant treatments, survival outcomes. If outcomes were reported in multiple data sets, the one with more adjusted confounders will be used. All disputes in the process of data extraction will be resolved through team negotiation.

**Dealing with missing data**

To pool HRs of OS or DFS, when an HR and its upper or lower limit of 95% CI are provided by a trial, we can calculate lnHR (the natural logarithm of HR) and its SE and then merge HRs. When the above data are incomplete, we will attempt to contact the authors to retrieve it. If do not get an effective response in 10 days, we will try to estimate some or all of the lnHR, the logrank observed minus expected events (O-E), the logrank variance and the variance of the lnHR by indirect methods. If even these indirect methods cannot be applied, we will consider to generate the necessary statistics from published Kaplan-Meier curves. When a trial fails to provide necessary statistics by mentioned methods, it will be omitted from pooling HRs. To pool ORs of 5-year OS rate or DFS rate, we will record data on the total number of participants and the incidence of events in each arm of every trial. When these data in the full text are incomplete, we will contact the authors to extract more, trials that fail to provide these necessary data will be excluded from pooling ORs.

**Risk of bias assessment**

Two independent reviewers (ZJ and ZC) will assess the methodological quality/risk of bias of included studies, disagreements will be resolved by discussion, where necessary, in consultation with the third reviewer (YY). For RCTs, the risk of bias will be assessed using the Cochrane Collaboration’s risk of bias tool. For NRS, we will use the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool. Results of this meta-analyses will be interpreted in light of risk of bias assessment of the included studies.

**Measurements**

As for time-to-event outcome, the HR will be used to pool overall effects. Dichotomous outcome will be analysed by calculating the OR. Results will be presented as summary relative effect sizes (HR or OR) with 95% CIs.

**Strategy for data synthesis**

We will import extracted data into Rev Man V.5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) for data synthesis by the first reviewer and checked by the second one. The overall pooled estimates for the association between resection margin status and survival will be calculated in the meta-analysis. Due to the nature of survival analysis, we will first try to extract HR-related data from each included study and then estimate pooled HRs for OS and DFS with 95% CI according to methods introduced by Parmar et al and Tierney et al. If multiple HRs for a same outcome are presented in a paper, we will choose the one adjusted for the greatest number of confounders. Subsequently, we will try to extract the 5-year OS rate and DFS rate of the two groups from each included study and estimate pooled ORs with 95% CI. NRS with large sample sizes pooling with small RCTs could dominate the pooled effect estimates, thus we will perform data synthesis separately for RCTs and NRS. Statistical heterogeneity will be assessed by visual inspection of forest plots and measured using the I² statistics. I² < 50% or ≥50% indicates low or high heterogeneity, respectively. A fixed effect model will be used when heterogeneity is low, otherwise, a random
effect model will be chosen. When substantial heterogeneity is detected, subgroup analysis and sensitivity analysis will be performed to investigate its possible sources. In case of considerable clinical heterogeneity, a narrative review rather than meta-analysis will be conducted.

**Sensitivity analysis and subgroup analyses**

We will apply the leave-one-out sensitivity analysis to evaluate the robustness of the results.

Subgroup analyses are planned as follows:
1. Study carried out in: Asia and other regions.
2. Tumour stage: early gastric cancer and advanced gastric cancer.
3. Lymphadenectomy: ≤D1 and ≥D2.
4. HR (estimating OS or DFS) extracted from: multivariate analysis and univariate analysis.
5. Proximal cancer (tumour in the gastro-oesophageal junction, cardia or fundus).

**Publication bias assessment**

Since detecting and overcoming publication bias are problematic and firm guidance is not yet offered, we will use visual inspection of funnel plots to assess publication bias, with results being interpreted cautiously.

**Quality of the evidence**

Two reviewers (ZC and YY) will assess overall quality of evidence for each outcome independently using the five Grading of Recommendations, Assessment, Development and Evaluations (GRADE) considerations. In this approach, direct evidence from RCTs begins at high quality, while observational study begins at low; however, the overall quality will be analysed on five down-grade considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) and three up-grade considerations (large magnitude of effect, dose–response relation and plausible confounders or biases), and finally rate it as high, moderate, low or very low.

Disagreements will be solved by discussion. Whenever necessary, we will provide all decisions to down grade or up grade the quality of studies with clear arguments in footnotes to aid the reader’s understanding of the table and the process.

**Presentation and reporting of results**

We will summarise the study selection process by a flow diagram with reasons for exclusions (figure 1). The characteristics of each included study will be tabulated in detail. We will use forest plots to present the pooled

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**Table 2 Data extraction form**

| Study details |  |
|---|---|
| **General information** |  |
| First author |  |
| Year of publication |  |
| Region |  |
| Study period |  |
| Study eligibility |  |
| Study design |  |
| Participants |  |
| Exposure |  |
| Control |  |
| Outcome diagnostic criteria |  |
| Confounding variables |  |
| Include or exclude | Include □ exclude □ |
| Reason(s) for exclusion |  |
| **Characteristics of included studies** |  |
| Sample size |  |
| R1 margin group |  |
| R0 margin group |  |
| Data source |  |
| Age (mean or median) |  |
| Gender (male rate) |  |
| Follow-up (mean and range) (months) |  |
| R1 margin rate (%) |  |
| R0 margin rate (%) |  |
| Tumour size (cm) |  |
| Tumour site |  |
| Tumour stage |  |
| Histologic grade |  |
| Type of surgery |  |
| Lymphadenectomy |  |
| Neoadjuvant or adjuvant treatment for R1 margin group |  |
| Neoadjuvant or adjuvant treatment for R0 margin group |  |
| Subgroups |  |
| Key conclusion(s) |  |
| **Primary outcomes** |  |
| HRs (comparing R1 and R0 group) with 95% CI |  |
| OS |  |
| DFS |  |
| Relevant data to calculate HRs |  |
| OS |  |
| DFS |  |
| Other data |  |
estimates. Additionally, for each outcome, ‘summary of findings’ tables compiled by GRADEpro software (GRADEpro GDT 2015) will be presented separately for both RCTs and NRS.

**Patient and public involvement**

This systematic review and meta-analysis will be based on published studies, raw patient data will not be collected. As a result, patients and the public will not be involved in the design, or conduct, or reporting or dissemination plans of this research.

**Ethics and dissemination**

There is no ethics approval required for this systematic review due to no patient data being collected at an individual level. We will seek to present the findings of this systematic review at relevant conferences and publish in an influential open access journal, any deviations from the protocol will be clearly documented and explained in its final report.

**SUMMARY**

This is a protocol for a systematic review and meta-analysis reported according to the PRISMA-P guidelines. This systematic review and meta-analysis will explore the influence of R1 margin comparing with R0 margin on gastric cancer survival by summarising the published studies and reveal which subgroups are most affected by R1 margin and which are not. It will be conducted according to PRISMA guidelines and with robust methodological processes and statistical analyses. Risk of bias will be evaluated at study level using Cochrane Collaboration’s risk of bias tool and ROBINS-I tool as well as at outcome level using the GRADE approach. As a result, its findings might provide relevant evidence and help surgeons to determine whether their patients with R1 margins need resections or other aggressive treatments.

Contributors The original idea of this research was conceived by BZ, JZ and ZC designed the protocol and drafted the manuscript. JZ, ZC, YY and CS participated in developing the eligibility criteria, search strategy, data extraction methods and data summary plan. JZ, ZC and JH will search for studies, extract and analyse the data. BZ and YYQ supervised the work. All authors approved the final version of this manuscript.

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**Competing interests**

None declared.

**Patient consent for publication**

Not required.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

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