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Neoadjuvant and/or adjuvant chemotherapy for gastric cancer patients with microsatellite instability or deficient mismatch repair: a systematic review and meta-analysis study protocol

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ABSTRACT

Introduction Whether gastric cancer (GC) patients with deficient mismatch repair or microsatellite instability-high (dMMR/MSI-H) benefit from perioperative (neoadjuvant and/or adjuvant) chemotherapy is controversial. This protocol delineates the planned scope and methods for a systematic review and meta-analysis that aims to compare the efficacy of perioperative chemotherapy with surgery alone in resectable dMMR/MSI-H GC patients.

Methods and analysis This study protocol is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols-P guideline. PubMed, Embase, Cochrane (CENTRAL), and the Web of Science databases will be searched, supplemented by a secondary screening of relevant records. Both randomised controlled trials and non-randomised studies will be included in this study. The primary and secondary outcomes under scrutiny will be overall survival, disease-free survival and progression-free survival. Two reviewers will independently screen studies, extract data and assess the risk of bias. We will analyse different treatment settings (eg, neoadjuvant or adjuvant or combined as perioperative chemotherapies) separately and conduct sensitivity analyses.

Ethics and dissemination No ethics approval is required for this systematic review and meta-analysis, as no individual patient data will be collected. The findings of our study will be published in a peer-reviewed journal.

Prospero registration number CRD42023494276.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This protocol ensures that we are transparent with the whole process for this study to reduce the possibility of duplication as well as potential bias in our study.
⇒ Several subgroups (stages II and III) and sensitivity (using multivariable-adjusted results) analyses will boost the robustness of our study.
⇒ The Cochrane Collaboration's tool and Risk of Bias In Non-randomised Studies of Interventions tool will be used to evaluate the quality of evidence and provide comprehensive references to clinical recommendations.
⇒ The heterogeneities among chemotherapy regimens may limit the evidence quality.
⇒ Our results may be limited by the quality of eligible studies included.

INTRODUCTION

Gastric cancer (GC) ranks as the fourth leading cause of cancer-related death worldwide, which accounted for ~770 000 deaths globally in 2020 and is projected to increase to 1.3 million deaths by 2040.[1] Surgical resection is the primary curative treatment for patients diagnosed at an early stage., While for patients with locally advanced GC, the fluoropyrimidine and/or platinum-based perioperative (neoadjuvant and/or adjuvant) chemotherapy has been established as the standard of care in clinical management, which significant prolonged the overall survival (OS) compared with surgery alone.[2–6] However, approximately 40–60% of GC patients who undergo curative resection and perioperative chemotherapy still experience relapse or metastasis.[7–9] Thus, there is a crucial need for identifying patients who may or may not benefit from perioperative chemotherapy.

Recent advancements in molecular research have significantly enhanced our comprehension of the underlying mechanisms and intrinsic characteristics of GC at the genomic, transcriptomic and protein expression levels. Several molecular subtyping systems have been proposed based on these findings. Notably, the microsatellite instability (MSI) subtype has been independently validated by two large consortiums, the Cancer Genome Atlas[10] and Asian Cancer Research Group,[11] and account for

approximately 10–22% of the total GCs.[10 12] MSI arises from deficiency in DNA mismatch repair (dMMR) function, either through germline mutations in the genes encoding the MMR enzymes (MLH1, MSH2, MSH6 or PMS2) or via somatic hypermethylation of the MLH1 promoter.[13 14] These results in high tumour mutation burden and genetic hypermutability, known as microsatellite instability-high (MSI-H). In recent years, increasing attention has been focused on the debatable question of whether dMMR/MSI-H could serve as a marker of response to perioperative chemotherapy.

Based on the post hoc analysis of the MAGIC[15] and CLASSIC[16] randomised trial, GC patients with a dMMR/MSI-H status did not benefit from perioperative and adjuvant chemotherapy, or even with a harmful effect. These results were further validated by an individual patient data (IPD) meta-analysis by combining four randomised trials (MAGIC, CLASSIC, ARTIST and ITACA-S).[17] However, a retrospective analysis from Kim *et al*, comprising of 157 MSI-H GC patients revealed that adjuvant chemotherapy improved disease-free survival (DFS) and OS after adjusting for gender, age and pathological type.[18] Similarly, Boyers *et al* also suggest a better outcome in dMMR/MSI-H gastro-oesophageal cancer patients who received chemotherapy.[19] More recently, emerging studies, including one prospective analysis, that compare perioperative chemotherapy with surgery alone in dMMR/MSI-H GC patients have been published.[20–22] Meanwhile, a previous meta-analysis only focused on adjuvant chemotherapy in dMMR/MSI-H patients and the number of studies (n=7) included is limited.[23]

Thus, to summarise the conflicting evidence regarding the efficacy of perioperative chemotherapy in GC patients with dMMR/MSI-H, we aim to conduct a systematic review and meta-analysis (including the stratification analyses of neoadjuvant or adjuvant settings separately). Because only a small fraction of dMMR/MSI-H GC patients in the overall GC population may limit the explanation of studies from a single institute, we believe our study will significantly improve the total sample size of dMMR/MSI-H GC patients in the analysis. The findings derived from this study will provide further evidence for precision clinical management of GC and may contribute to future clinical recommendations.

METHODS AND ANALYSIS

Protocol and registration

The current protocol has been registered with the PROSPERO platform (CRD42023494276) and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidelines[24] (PRISMA-P checklist included in online supplemental file 1. This systematic review and meta-analysis will be reported according to the PRISMA 2020 statement and will adhere to the standard methodology recommended by the Cochrane Collaboration.[25–27]

Inclusion criteria

The inclusion criteria are described under the population, intervention, comparators, outcomes and study design framework.[28] There will be no limitations on language or publication year. The inclusion criteria for studies are as follows:

Population: Patients diagnosed with GC based on a histological examination. All patients will be considered, without restrictions based on country/region, ethnicity, age, gender or occupation.

Intervention: Underwent surgery with curative intent and with perioperative chemotherapy (including neoadjuvant and/or adjuvant chemotherapy). In addition, neoadjuvant or adjuvant chemotherapy will be analysed separately. All regimens of chemotherapy will be considered.

Comparison: Surgery alone.

Outcomes and measurement: The primary outcome is the OS, which is defined as the time to death from any cause. Secondary outcomes are DFS, defined as the time to recurrence of disease (or death) after curative-intent surgery, or progression-free survival (PFS), defined as the time to progression or death. We will present time-to-event data as the HR with 95% CI.

Study design: Suitable study designs will encompass non-randomised studies (NRS) such as case-control studies and cohort studies, as well as randomised controlled trials (RCTs).

Other inclusion criteria: Eligible studies must have a minimum of 24 months of follow-up, reporting survival (time-to-event) outcomes. Additionally, these studies need to provide adequate data to compute or estimate HR and 95% CI.

Exclusion criteria

The exclusion criteria include the following: (1) studies with overlapping populations or results; (2) meeting abstracts, letters, case reports/series, reviews or non-clinical studies lacking available data; (3) patients received the intervention other than chemotherapy, such as chemoradiotherapy; (4) patients received palliative resections; (5) data are missing or cannot be retrieved after reasonable contact with the corresponding author; (6) article full-text cannot be acquired.

Information sources and search strategy

We will systematically search the PubMed, Embase, Cochrane (CENTRAL) and Web of Science databases from their inception up to 1 March 2024. The specific search strategy for each database is listed in online supplemental file 2. Additionally, we will manually review the references of all included articles to identify further studies that meet the eligibility criteria, and their full texts will be obtained.

Study selection and data extraction

All retrieved study records will be imported into Zotero software (https://www.zotero.org/). After removing duplicates, two reviewers will independently evaluate all articles based on the specified eligibility criteria. Initially,

the two reviewers will screen titles and abstracts. Then, they will independently reassess the full texts of the identified studies, confirming the rationale for inclusion and exclusion. The screening process will be presented in a PRISMA flow diagram.[25]

Data extraction for the included studies will be independently conducted by two authors using a standardised electronic data extraction form that has been discussed and agreed upon by all reviewers. The following information will be extracted, such as country/region, chemotherapy regimens, outcomes and median follow-up time. Of note, when multiple studies are conducted on the same subjects and report the same outcomes, only the study with the largest number of cases will be included. Any discrepancies during the process of study selection and data extraction will be resolved through team discussion.

Dealing with missing data

In cases where a study does not provide the HR and its 95% CI, we will reach out to the corresponding author via email to request the missing data. If no response is received within 7 days, we will attempt to estimate some or all of the lnHR, the log-rank observed minus expected events (O-E), the log-rank variance and the variance of the lnHR using indirect methods.[29] Of note, when multiple groups were analysed in one study, and the HR for the intervention and comparison group were reported using another group as a reference, the HR and its 95% CI for the intervention group (using the comparison group as a reference) will be calculated as suggested by Woods *et al*.[30] If these indirect methods are also inapplicable, we will estimate HR based on Kaplan-Meier curves using IPDfromKM (https://biostatistics.mdanderson.org/shinyapps/IPDfromKM/)[31] or KMtoIPD[32] in R software. Generally, if Kaplan-Meier curves and the information of the number at risk were available, IPD would be extracted using graph digitizer software (WebPlotDigitizer V.4.6, https://github.com/ankitrohatgi/WebPlotDigitizer). Next, the output data from WebPlotDigitizer will be uploaded in the IPDfromKM platform or KMtoIPD in R software to estimate the HR and 95%CI by using Cox proportional hazard regression models.[33]

Risk of bias assessment

Two separate reviewers will appraise the methodological quality and potential bias of the incorporated studies. Any discrepancies will be addressed through team discussions. RCTs will undergo a risk of bias evaluation using the Cochrane Collaboration tool.[34] NRS will be evaluated using the Risk of Bias In Non-randomised Studies of Interventions tool.[35]

Assessment of publication biases

Funnel plots will be applied to investigate potential publication bias if more than 10 studies were pooled in an analysis. To ascertain the statistical significance of publication bias, we will employ Egger's test, and a p-value <0.05 is indicative of a statistically significant publication bias.

Data analysis

For feasible studies, the collected data will be analysed using RevMan software (V.5.4.1). Time-to-event outcomes will be assessed by pooling HR and their corresponding 95% CI. A two-sided p<0.05 will be considered statistically significant. Unless otherwise specified, HR derived from multivariate analysis will be included by default. In the absence of multivariate values, univariate data will be employed.

Heterogeneity will be examined using the Cochrane Q-test, and the I^2 statistic. Significance for heterogeneity was defined as a p-value <0.10 and an I^2 statistic >50%. Anticipating a certain degree of heterogeneity among studies, we will employ a random-effects model as a default approach. Our assumption is that the studies to be included are not uniformly estimating the same intervention effect, and these intervention effects are expected to conform to a normal distribution across the studies.[36] Furthermore, an analysis of the included studies will consider their design and characteristics. This study will start on 1 March, and the expected end time is 1 July.

A priori subgroup analyses

If there are multiple studies presenting homogeneous outcomes within the specified subgroups, the planned subgroup analyses (perioperative chemotherapy in stage-II and stage-III diseases) for the primary and secondary outcomes will be conducted. Given the chemotherapeutic cycles ranging from 2 to 6 for neoadjuvant or adjuvant chemotherapy,[37] and the duration of chemotherapy may influence the efficacy. Thus, we plan to conduct a subgroup analysis based on different therapy cycles (ie, no more than two cycles and more than two cycles of chemotherapy in neoadjuvant and/or adjuvant settings) if relevant data are provided.

Sensitivity analysis

Given the potential impact of confounding factors such as age, gender, histopathological type and tumour stage that may influence the interpretation of results in the individual analysis, a sensitivity analysis will be performed by including only studies reporting the results from multivariable analyses that are adjusted for the aforementioned factors. If the number of studies that need to be estimated is relatively large (>50%), sensitivity analysis will be conducted using only reported data from original studies.

DECLARATIONS

Ethics and dissemination

No ethics approval is required for this systematic review and meta-analysis, as no individual patient data will be collected. The findings of our study will be published in a peer-reviewed journal.

Contributors BL and YY conceptualised this research. BL, XY, ZC, CS, TJ and YH contributed to the formulation of eligibility criteria, development of the search strategy, design of data extraction methods and the plan for data analysis strategies. BL and XY registered the protocol on the PROSPERO platform and drafted the manuscript. The manuscript underwent review and revision by BZ and YY. The final version of the manuscript received approval from all authors.

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Competing interests None declared.

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

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Supplementary file 1.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Pages
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	-
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	10
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
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	-
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	10
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	10

INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
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	7 and supplementary file 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7-8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	6
Outcomes and	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6

prioritization			
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	8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9
	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 (such as I^2, Kendall's τ)	9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7-8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	5

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplementary file 2. Search strategies for different databases.

PubMed search terms:

("gastric cancer"[tiab] OR "gastric carcinoma"[tiab] OR "stomach cancer"[tiab] OR "stomach adenocarcinoma"[tiab] OR "gastro-oesophageal cancer"[tiab] OR "gastro-oesophageal junction cancer"[tiab] OR "gastro-oesophageal carcinoma"[tiab] OR "gastro-oesophageal junction carcinoma"[tiab]) AND ("microsatellite instability"[MeSH Terms] OR "microsatellite instability"[tiab] OR "MSI"[tiab] OR "MSI-H"[tiab] OR "BAT25"[tiab] OR "BAT26"[tiab] OR "D5S346"[tiab] OR "D2S123"[tiab] OR "D17S250"[tiab] OR "mismatch repair deficiency"[tiab] OR "deficient mismatch repair"[tiab] OR "dMMR"[tiab] OR "MMRd"[tiab] OR "MLH1"[tiab] OR "MSH2"[tiab] OR "MSH6"[tiab] OR "PMS2"[tiab]) AND ("Chemotherapy, Adjuvant"[MeSH Terms] OR "Neoadjuvant Therapy"[MeSH Terms] OR "chemotherapy"[tiab])

EMBASE search terms:

('gastric cancer':ab,ti OR 'gastric carcinoma':ab,ti OR 'stomach cancer':ab,ti OR 'stomach adenocarcinoma':ab,ti OR 'gastro-oesophageal cancer':ab,ti OR 'gastro-oesophageal junction cancer':ab,ti OR 'gastro-oesophageal carcinoma':ab,ti OR 'gastro-oesophageal junction carcinoma':ab,ti) AND ('microsatellite instability':ab,ti OR 'MSI':ab,ti OR 'MSI-H':ab,ti OR 'BAT25':ab,ti OR 'BAT26':ab,ti OR 'D5S346 ':ab,ti OR 'D2S123':ab,ti OR 'D17S250':ab,ti OR 'deficient mismatch repair':ab,ti OR 'mismatch repair deficiency':ab,ti OR 'dMMR':ab,ti OR 'MMRd':ab,ti OR 'MLH1':ab,ti OR 'MSH2':ab,ti OR 'MSH6':ab,ti OR 'PMS2':ab,ti) AND ('chemotherapy':ab,ti) AND 'human'/de AND ('article'/it OR 'article in press'/it)

Cochrane Central Register of Controlled Trials (CENTRAL) search terms:

#1 ((gastric cancer) OR (gastric carcinoma) OR (stomach cancer) OR (stomach adenocarcinoma) OR (gastro-oesophageal cancer) OR (gastro-oesophageal junction cancer) OR (gastro-oesophageal carcinoma) OR (gastro-oesophageal junction carcinoma):ti,ab,kw) 12114
#2 MeSH descriptor: [Stomach Neoplasms] explode all trees
#3 #1 OR #2
#4 ((microsatellite instability) OR (MSI) OR (MSI-H) OR (BAT25) OR (BAT26) OR (D5S346) OR (D2S123) OR (D17S250) OR (deficient mismatch repair) OR (mismatch repair deficiency) OR (dMMR) OR (MMRd) OR (MLH1) OR (MSH2) OR (MSH6) OR (PMS2):ti,ab,kw)
#5 MeSH descriptor: [Microsatellite Instability] explode all trees
#6 #4 OR #5
#7 (chemotherapy):ti,ab,kw
#8 MeSH descriptor: [Chemotherapy, Adjuvant] explode all trees
#9 MeSH descriptor: [Neoadjuvant Therapy] explode all trees
#10 #7 OR #8 OR #9
#11 #3 AND #6 AND #10

Web of Science search terms:

TS=("gastric cancer" OR "gastric carcinoma" OR "stomach cancer" OR "stomach adenocarcinoma" OR "gastro-oesophageal cancer" OR "gastro-oesophageal junction cancer" OR "gastro-oesophageal carcinoma" OR "gastro-oesophageal junction carcinoma") AND TS=("microsatellite instability" OR "MSI" OR "MSI-H" OR " BAT25" OR " BAT26" OR " D5S346" OR " D2S123" OR "D17S250" OR "deficient mismatch repair" OR "mismatch repair deficiency" OR "dMMR" OR "MMRd" OR "MLH1" OR "MSH2" OR "MSH6" OR "PMS2") AND TS=("chemotherapy") AND DT=(Article)