INPLASY PROTOCOL

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Conflicts of interest:
There is no conflict of interest.

Clinical efficacy of adjuvant chemotherapy in the treatment of pT4 Stage II Colorectal Cancer with defective Mismatch Repair status. A protocol for systematic review and meta-analysis

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Review question / Objective: **P: pT4 stage II colorectal cancer patients with defective Mismatch Repair status; I: adjuvant chemotherapy; C: adjuvant chemotherapy vs observation; O: prognostic effectiveness; S: RCTs.**
Condition being studied: **pT4 stage II colorectal cancer.**
Information sources: **A systematic search of PubMed, EMBASE, Web of science, Cochrane Library databases will be performed. And the included references, academic conferences and network resources in the literature were inquired at the same time to find out the research that may meet the inclusion criteria. All Randomized controlled trials (RCT) published in electronic databases from inception to March 19, 2020, with language restricted in English will be included in this review study. We will manage all references and duplicates using EndNote X9 citation management software. the clinical problems were refined by the principle patient, intervention, contrast, outcome, study (PICOS).**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 05 May 2020 and was last updated on 05 May 2020 (registration number INPLASY202050019).

INTRODUCTION

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METHODS

Search strategy: **The Medical Subject Headings (MeSH), text words, and word**

variants for "T4N0M0" ,"pT4", "T4","stage 2", "stage II", "colorectal cancer", "colorectal neoplasms", "dMMR", "MSI-H" ,"dMMR/MSI-H", "defective Mismatch Repair ","high-risk", "adjuvant chemotherapy" ,"post-operative chemotherapy", "prognostic" , "prognosis", "overall survival", "OS", "progression free survival" and "PFS" are used and combined in the searches. This search strategy will be modified to be suitable for other electronic databases.

Participant or population: It included patients who underwent radical resection and dMMR pT4 stage II CRC was confirmed by pathologic or histologic examination after surgery. The tumor that yielded negative staining results for at least one of the MMR proteins, MLH1, MSH2, MSH6, PSM6 were classified as dMMR tumors, and all others were classified as pMMR tumors.

Intervention: Receiving adjuvant chemotherapy . There will be no restrictions on the type, dose, frequency of adjuvant chemotherapy. The control group (observation group) will not receive any type of adjuvant chemotherapy. Studies to compare the effect of different adjuvant chemotherapy strategies without only observation group will be excluded.

Comparator: Observation after radical resection of colorectal cancer.

Study designs to be included: RCTs.

Eligibility criteria: (1) Patients who underwent radical resection of CRC, and pT4 stage II CRC with dMMR status was confirmed by pathologic or histologic examination after surgery; (2) the article assessed the relationship between patients receiving ACT and observation and assess overall survival (OS) and disease- free survival (DFS); (3) full text in English; and (4) sufficient information to extract hazard ratios (HRs) and their 95% con- fidence intervals (CIs).

Information sources: A systematic search of PubMed, EMBASE, Web of science, Cochrane Library databases will be performed. And the included references, academic conferences and network resources in the literature were inquired at the same time to find out the research that may meet the inclusion criteria. All Randomized controlled trials (RCT) published in electronic databases from inception to March 19, 2020, with language restricted in English will be included in this review study. We will manage all references and duplicates using EndNote X9 citation management software. the clinical problems were refined by the principle patient, intervention, contrast, outcome, study (PICOS).

Main outcome(s): The primary outcomes consisted of overall survival (OS), progression-free survival (PFS) and sufficient information to extract hazard ratios (HRs) and their 95% confidence intervals (CIs).

Additional outcome(s): Secondary outcomes consisted of other clinical and pathological high-risk factors, included intestinal perforation, intestinal obstruction, fewer than 12 sample of lymph nodes, lymphovascular invasion (LVI), perineural invasion (PNI), poor differentiated histology and close or indeterminate or positive margins.

Data management: We will manage all references and duplicates using EndNote X9 citation management software.

Quality assessment / Risk of bias analysis: The quality of evidence of outcomes will be assessed by two authors(LBH and THY) according to the "Bias Risk Assessment" tool recommended by Cochrane Collaboration Network (Version 5.1.0) which include selection bias (method of randomization and allocation concealment), information bias (masking of outcome adjudicators), and bias in the analysis (intention to treat analysis and completeness of follow-up). The strength of the body of evidence will be graded into 3 levels, "High Risk", "Low Risk", "Unclear". Disagreement which existed between two author's results will be solved

by discussion and settled through consultation with the third party (CW). Bias risk assess figure will be drawn by RevMan software 5.3.

Strategy of data synthesis: We will employ the RevMan software 5.3 software to evaluate the correlations between intervention and OS and DFS using HRs and 95%CIs. If HRs and 95%CIs cannot be obtained from the original study, we will figure out these values using the methods reported by Parmar et al15 and Tierney et al16. The heterogeneity will be analyzed before meta-analysis, we will use I2 statistics to assess heterogeneity across included studies. If p-value $<$0.10 and/or I2 $<$50%, it indicate that the heterogeneity among included studies were small we will pool data across studies using fixed-effects model for meta-analysis. If I2 $>$ 50%, we will use random-effects model to make meta-analysis, and Sensitivity analysis or subgroup analysis is needed to identify the sources of heterogeneity among the included studies. And the two-side p value $<$ 0.05 in Z-test will be considered as statistically significant.

Subgroup analysis: We will perform subgroup analysis to find out heterogeneity parameters. Subgroup analysis will be done based on sex, age, intestinal perforation, intestinal obstruction, fewer than 12 sample of lymph nodes, lymphovascular invasion (LVI), perineural invasion (PNI), poor differentiated histology and close or indeterminate or positive margins.

Sensibility analysis: In order to ensure the stability of primary outcome, we will perform sensitivity analysis by excluded those studies with high risk of bias according to the sample size, study design, heterogeneity qualities, and statistical model (random-effects or fixed-effects model) and with non-informative prior distributions for the heterogeneity parameters. If result of sensitivity analysis is quite different from meta-analysis, it should be considered to make a descriptive analysis.

Language: English.

Country(ies) involved: China.

Keywords: Stage II colorectal cancer; high-risk factor; dMMR; adjuvant chemotherapy; meta-analysis; protocol.

Contributions of each author:

Author 1 - Li-Bin Huang - Planned and designed the research. tested the feasibility of the study. provided methodological advice, polished and revised the manuscript. wrote the manuscript. approved the final version of the manuscript.

Author 2 - Ting-Han Yang - Planned and designed the research. tested the feasibility of the study. provided methodological advice, polished and revised the manuscript. wrote the manuscript. approved the final version of the manuscript.

Author 3 - Lie Yang - Tested the feasibility of the study. provided methodological advice, polished and revised the manuscript. approved the final version of the manuscript.

Author 4 - Yong-Yang Yu - Tested the feasibility of the study. provided methodological advice, polished and revised the manuscript.approved the final version of the manuscript.

Author 5 - Zi-Qiang Wang - Planned and designed the research. provided methodological advice, polished and revised the manuscript.approved the final version of the manuscript.

Author 6 - Cun Wang - Planned and designed the research. tested the feasibility of the study. provided methodological advice, polished and revised the manuscript. wrote the manuscript. approved the final version of the manuscript.

Author 7 - Zong-Guang Zhou - Planned and designed the research. provided methodological advice, polished and revised the manuscript. approved the final version of the manuscript.