INPLASY PROTOCOL

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There is no conflicts of interest to declare.

Oncologic outcomes of intersphincteric versus abdominoperineal resection for lower rectal cancer: A protocol for systematic review and meta-analysis

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Review question / Objective: **P: resectable lower rectal cancer (LRC) patients; I: intersphincteric resection (ISR); C: abdominoperineal resection (APR); O: oncologic outcomes; S: randomized controlled trials (RCTs) and quasi-RCTs.**
Condition being studied: **Rectal cancer accounts for approximately 40% of Colorectal cancer (CRC) and constitutes a severe global public health burden. Due to the specific nature of anatomy, lower rectal cancer (LRC) located within 5 cm from the anal verge (AV) is always the clinical key and difficult point. Abdominoperineal resection (APR) has long been considered a standard surgical procedure for LRC and markedly improved patient survival. As the APR procedure requires permanent colostomy, concerns for post-operative health-related quality of life (HRQOL) as well as widespread adoption of neoadjuvant chemoradiation therapy (nCRT) and technical advances in tumor resection and device-assisted anastomosis have allowed for the development of sphincter-preserving procedures (SPPs) for LRC. The revolutionary intersphincteric resection (ISR) with coloanal anastomosis aimed for radical tumor resection combined with sphincter preservation for LRC patients. However, whether ultimate sphincter-preserving procedure, ISR, offers an equal or better local control and survival benefit to patients with LRC is still under heated debate compared to APR.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 August 2020 and was last updated on 27 August 2020 (registration number INPLASY202080111).

INTRODUCTION

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METHODS

Search strategy: The search strategy on PubMed was as follows: #1 (((((((rectal neoplasm) OR rectum neoplasm) OR rectal tumor) OR cancer of rectum) OR rectum cancer) OR rectal cancer) OR rectum cancer) OR cancer of the rectum #2 (((intersphincteric resection) OR intersphincteric excision) OR intersphincter resection) OR intersphincter excision #3 (((((((abdominoperineal resection) OR abdominoperineal excision) OR abdomino-perineal resection) OR abdomino-perineal excision) OR abdominoperineal rectum excision) OR abdomino-perineal rectum excision) OR abdominoperineal proctectomy) OR abdomino-perineal proctectomy) OR Miles #4 ((((((((“Randomized Controlled Trial” [Publication Type]) OR “Controlled Clinical Trial” [Publication Type]) OR “randomized” [tiab]) OR “placebo” [tiab]) OR “Clinical Trials as Topic”[Mesh: NoExp]) OR “randomly” [tiab]) OR “trial” [ti])) NOT ((“Animals” [mh]) NOT “ humans” [mh]) #5 #1 AND (#2 OR #3) AND #4 This search strategy was modified to be suitable for other certain electronic databases.

Participant or population: Patients with pathologically proven rectal cancer located within 5 cm from the anal verge (AV) on colonoscope or magnetic resonance imaging (MRI).

Intervention: Intersphincteric resection as established by Schiessel in 1994 with or without protective ileostomy, including partial, subtotal and total ISR. Open, laparoscopic- and robotic-assisted approaches met the inclusion criteria.

Comparator: Conventional abdominoperineal resection as proposed by WE Miles in 1908. Open, laparoscopic- and robotic-assisted approaches met the inclusion criteria.

Study designs to be included: RCTs and quasi-RCTs.

Eligibility criteria: 1) Patients with pathologically proven rectal cancer located within 5 cm from the anal verge (AV); 2) Patients were randomly assigned into intersphincteric resection (ISR) and abdominoperineal resection (APR) group in the eligible RCT studies; 3) Oncologic outcomes, including circumferential resection margin (CRM) involvement, local recurrence (LR), disease-free survival (DFS), local recurrence-free survival (LFS) and overall survival (OS), were assessed in the eligible studies; 4) Available full-text with language restricted in English; 5) Sufficient data to extract odds ratios (ORs), hazard ratios (HRs) and relevant 95% confidence intervals (CIs).

Information sources: A systematic literature search in PubMed, MEDLINE, Excerpta Medica Database (EMBASE), Web of science, and the Cochrane Library databases was performed. The Cochrane Central Register of Controlled Trials, International Clinical Trials Registry Platform (ICTRP), clinicaltrials.gov,

clinicaltrialsregister.eu and controlledtrials.com were also searched for ongoing trials. The relative references, academic conferences and network resources in the included literature were also further screened for potential eligible ones. When multiple reports describing the same sample were published, the most recent or complete report was included. All RCTs published in electronic databases through May 20, 2019 with language restricted in English were included in this review study.

Main outcome(s): 1) circumferential resection margin (CRM) involvement; 2) local recurrence (LR); 3) disease-free survival (DFS); 4) local recurrence-free survival (LFS); 5) overall survival (OS).

Data management: EndNote X9 software (Clarivate Analytics) was employed to manage all citations, as well as for duplicates screening. Stata software version 14.0 (Stata Corp LP, College Station, TX) will be used to carry out main statistical analyses.

Quality assessment / Risk of bias analysis: The methodological quality of included studies was assessed by two authors utilizing the Review Manager software version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) 'Risk of Bias' (RoB) assessment tool in terms of 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). Risk of bias for each study was quantified according to the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Disagreement between two reviewers was resolved by discussion and consulting an expert in Evidence-Based Medicine (EBM). The RoB table and graph were also drawn by RevMan 5.3.

Strategy of data synthesis: Stata v14.0 will be employed for main data syntheses. Dichotomous outcomes (CRM involvement and local recurrence) will be expressed as odds ratios (ORs) and relevant 95% confidence intervals (CIs). Continuous outcomes (DFS, LFS, and OS) will be expressed as Hazard ratios (HRs) with 95% CIs. HRs will be extracted from the reported values in studies or be estimated from Kaplan-Meier survival curves by established methods. The log hazard ratio (lnHR) and its relevant standard error (SE) will be calculated by approximating the data of the survival curve from original articles utilizing Engauge Digitizer version 4.1 (Free Software Foundation, Inc., Boston, Massachusetts, USA) and processing the data via the Calculations Spreadsheet in Microsoft Excel proposed by Tierney et al. The cutoff value representing statistical significance will be set at $p < 0.05$ to summarize the findings across the studies. Given potential between-study heterogeneity, pooled analyses will be conducted with a random effect model (REM) rather than fixed effect model (FEM). Statistical heterogeneity between studies will be evaluated using the chi-square test and quantified with Cochrane's Inconsistency-statistic. We set 50% as a cut-off value on heterogeneity, such that p-value <0.10 and/or $I > 50\%$ are considered substantial heterogeneity.

Subgroup analysis: Subgroup analyses will be conducted to identify possible sources of heterogeneity based on sex, age, region (Eastern and Western countries), T substage, median distance of tumor from anal verge, and neoadjuvant chemoradiation therapy.

Sensibility analysis: The sensitivity analysis will be performed to ensure the stability of measure effects of the main outcomes by removing one by one those included studies with suspected high risk of bias in terms of sample size, study design, heterogeneity qualities, and with non-informative prior distributions for the heterogeneity parameters. Non-robust results of the main outcomes identified by sensibility analysis will be added to a descriptive analysis.

Language: Only articles originally written in English or translated into English will be considered.

Country(ies) involved: China.

Keywords: Lower rectal cancer; Intersphincteric resection; Abdominoperineal resection; Hazard ratio; Oncologic outcome.

Contributions of each author:

Author 1 - Wenming Yang - The author devised the research, identified the feasibility of the study, and drafted the manuscript.

Author 2 - Jianhao Zhang - The author devised the research, identified the feasibility of the study, and contributed equally to draft the manuscript with Author 1.

Author 3 - Zida Ma - The author contributed to the study design, development of the selection criteria, and risk of bias assessment and reviewed the final version of the manuscript.

Author 4 - Xueting Liu - The author provided methodological advice and statistical expertise, and reviewed the final version of the manuscript.

Author 5 - Yongyang Yu - The author contributed to study design, provided feedback and approved the final version of the manuscript.

Author 6 - Lie Yang - The author planned and devised the research, identified the feasibility of the study, provided methodological advice, revised and polished the manuscript, and approved the final version of the manuscript.