

# INPLASY PROTOCOL

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None declared.

## Oncologic outcomes of intersphincteric resection vs. abdominoperineal resection for lower rectal cancer: a protocol for systematic review and meta-analysis

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**Review question / Objective:** P: lower rectal cancer (LRC) patients (The distance of lower tumor edge from the anal verge is less than 5 cm.); I: intersphincteric resection (ISR); C: abdominoperineal resection (APR); O: circumferential resection margin (CRM) involvement, local recurrence (LR), disease-free survival (DFS), local recurrence-free survival (LFS), and overall survival (OS). Objective: The aim of this study is to compare the oncologic outcomes for LRC patients after abdominoperineal resection (APR) and ISR through a meta-analysis.

**Information sources:** To compare APR with ISR in the management of LRC, a systematic electronic literature search was performed in databases of Cochrane Library, PubMed, EMBASE, MEDLINE, and International Clinical Trials Registry Platform (ICTRP) to identify relevant studies published prior to November 25, 2019.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 July 2021 and was last updated on 29 July 2021 (registration number INPLASY202170093).

### INTRODUCTION

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recurrence (LR), disease-free survival (DFS), local recurrence-free survival (LFS), and overall survival (OS). Objective: The aim of this study is to compare the oncologic outcomes for LRC patients after abdominoperineal resection (APR) and ISR through a meta-analysis.

**Condition being studied:** Colorectal cancer (CRC) is the fourth most commonly diagnosed malignancy and the second highest cause of cancer-related death worldwide. Rectal cancer accounts for approximately 40% of CRC and constitutes a severe global public health burden. Abdominoperineal resection (APR) has long been considered a standard surgical procedure for lower rectal cancer (LRC) located within 5 cm from the anal verge (AV) and markedly improved patient survival. As the APR procedure requires permanent colostomy, concerns for post-operative quality of life (QoL) in combination with technical advances in tumor resection and device-assisted anastomoses have allowed for the development of sphincter-preserving procedures (SPPs) for LRC. With the widespread adoption of neoadjuvant therapy and a total mesorectal excision (TME) surgical approach, management of LRC has shifted significantly. The revolutionary intersphincteric resection (ISR) with coloanal anastomosis, as established by Schiessel in 1994, aimed for radical tumor resection combined with sphincter preservation for LRC patients. Then various studies emerged reporting single- or multi-institutional experience on ISR which has seemingly been proposed to achieve sphincter preservation without compromising local control or survival for tumors at or below 5 cm from AV. Pathologic assessment of the circumferential resection margin (CRM) and distal resection margin (DRM) of resected rectal tumor specimens is critical, as both CRM and DRM are powerful independent predictors of both local recurrence (LR) and survival. Several large-scale case series on resected rectal specimen indicated that APR was associated with a higher frequency of intraoperative tumor perforation (IOP) and CRM involvement and subsequently poorer survival compared with anterior resection (AR) due to insufficient standardization of safe surgical planes. Given the debate between APR and ISR as appropriate surgical management for LRC, this meta-analysis seeks to compare the oncologic outcomes following these two approaches.

## METHODS

**Search strategy:** The search was confined to studies published in English. The following search terms were used with Boolean operators AND, OR, and NOT: “rectal”, “cancer” or “carcinoma” or “malignancy”, “abdominoperineal resection” or “abdominoperineal excision”, “intersphincteric resection”, “sphincter-preserving” or “sphincter-saving” or “anus-sparing”. Related Medical Subject Headings (MeSH) were also searched. All references of included studies were reviewed to broaden the search for potential eligible studies. This meta-analysis was completed in compliance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline.

**Participant or population:** LRC patients (The distance of lower tumor edge from the anal verge is less than 5 cm).

**Intervention:** Intersphincteric resection (ISR).

**Comparator:** Abdominoperineal resection.

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

**Eligibility criteria:** The inclusion criteria for this meta-analysis were: patients with confirmed LRC by proctoscopy and histopathological findings; evaluation of both ISR and APR (open, laparoscopic, or robotic); inclusion of two or more primary outcomes of interest; reporting hazard ratios (HRs) or Kaplan-Meier curves with 95% confidence intervals (CIs); and full-text accessibility.

**Information sources:** To compare APR with ISR in the management of LRC, a systematic electronic literature search was performed in databases of Cochrane Library, PubMed, EMBASE, MEDLINE, and International Clinical Trials Registry Platform (ICTRP) to identify relevant studies published prior to November 25, 2019.

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**Main outcome(s):** Circumferential resection margin (CRM) involvement, local recurrence (LR), disease-free survival (DFS), local recurrence-free survival (LFS), and overall survival (OS).

**Quality assessment / Risk of bias analysis:** RCTs and quasi-RCTs were evaluated for quality by the Cochrane Risk of Bias (RoB) tool. Besides, to assess the methodological quality of included non-randomized controlled studies (NRCs), we used the Newcastle-Ottawa Scale (NOS) for cohort studies utilizing a star system to score studies from 0 (worst) to 9 (best) stars. Each included cohort study was evaluated on three dimensions: case selection (0-4 stars), comparability (0-2 stars), and outcome (0-3 stars).

**Strategy of data synthesis:** The Review Manager v5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used for statistical analyses. Odds ratio (OR) was chosen as an effect measure to compare dichotomous variables and hazard ratio (HR) was selected for survival analyses. The log hazard ratio (lnHR) and its relevant standard errors (SE) were calculated by approximating the data of the Kaplan-Meier survival curves included in original articles utilizing the Engauge Digitizer v4.1 (Free Software Foundation, Inc., Boston, Massachusetts, USA) and processing the data via the Calculations Spreadsheet in Microsoft Excel described by Tierney et al. A pooled HR estimate <1 demonstrated a better prognosis in the ISR group than in the APR group. And a P-value lower than 0.05 was defined as statistically significant and 95% confidence intervals (CIs) were provided for ORs or HRs. Considering heterogeneity between studies, pooled analyses were conducted with a random effect model (REM) rather than a fixed effects model.

**Subgroup analysis:** We will conduct subgroup analysis to reduce the unbalance of patients' characteristics, such as T stage, distance of lower tumor edge, and neoadjuvant therapy.

**Sensitivity analysis:** Statistical heterogeneity between studies was evaluated using the chi-square test and quantified with Cochrane's Inconsistency (I<sup>2</sup>)-statistic. We set 50% as a cut-off value, such that I<sup>2</sup> > 50% was considered substantial heterogeneity. If the presence of substantial heterogeneity was confirmed, we set up sensitivity analysis to explore possible causes for the heterogeneity.

**Language:** English.

**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 designed the research, identified the feasibility of the study, and drafted the manuscript.

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

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**Author 3 - Xueting Liu -** The author contributed to the study design and provided methodologic advices and statistical expertise, such as the development of the selection criteria and the risk of bias assessment strategy.

**Author 4 - Lie Yang -** The author planned and designed the research, identified the feasibility of the study, provided methodological advice, polished and revised the manuscript, and approved the final version of the manuscript.

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