INPLASY PROTOCOL

To cite: Yang et al. Comparative effectiveness of prophylactic hyperthermic intraperitoneal chemotherapy (HIPEC) for resected low-grade appendiceal mucinous neoplasm (LAMN). A protocol for systematic review and network meta-analysis. Inplasy protocol 202070112. doi: 10.37766/inplasy2020.7.0112

Received: 25 July 2020

Published: 25 July 2020

Corresponding author:
Wenming Yang

yangwenming94@163.com

Author Affiliation:
Department of Gastrointestinal Surgery, West China Hospital of Sichuan University, No. 37 Guoxue Lane, Chengdu, 610041, China.

Support: **Science & Technology Dept.**

Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
There is no conflicts of interest to declare.

Comparative effectiveness of prophylactic hyperthermic intraperitoneal chemotherapy (HIPEC) for resected low-grade appendiceal mucinous neoplasm (LAMN). A protocol for systematic review and network meta-analysis

Yang, WM[1]; Nie, P[2]; Liu, XT[3]; Peng, JK[4].

Review question / Objective: **P: low-grade appendiceal mucinous neoplasm (LAMN) patients after resection surgery; I: prophylactic hyperthermic intraperitoneal chemotherapy (HIPEC); C: follow-up and surveillance; O: prognostic effectiveness; S: randomized controlled trials.**
Condition being studied: **Appendiceal mucinous neoplasms (AMNs) are rare tumors that account for less than 2% of appendectomies. The World Health Organization classifies the majority of noninvasive epithelial lesions as low-grade appendiceal mucinous neoplasms (LAMNs). Histologically, LAMNs are characterized by well-differentiated adenomas that can proliferate outside the appendix in a biological malignant fashion. LAMNs may perforate and spread throughout the peritoneal cavity resulting in the distinctive and frequently aggressive syndrome called pseudomyxoma peritonei (PMP). Due to high relapse risk and unsatisfactory 10-year overall survival (OS) rate after treatment, PMP should be also regarded as malignancy. It is suggested that performing right hemicolectomy confers minimal survival benefit and is reserved for certain cases such as positive resection margins and lymph nodes after appendectomy or perforated appendix. Conversely, some medical centers advocate aggressive treatment approaches with prophylactic hyperthermic intraperitoneal chemotherapy (HIPEC) as an effective means to prevent development into widespread PMP. Thus, the aim of our meta-analysis is to investigate the comparative effectiveness and safety of enrolled prophylactic HIPEC regimens in patients with LAMNs after resection surgery. The results are expected to provide new evidences for more detailed individualized therapies for LAMNs.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 July 2020 and was last updated on 25 July 2020 (registration number INPLASY202070112).

INTRODUCTION

Review question / Objective: **P: low-grade appendiceal mucinous neoplasm (LAMN) patients after resection surgery; I: prophylactic hyperthermic intraperitoneal chemotherapy (HIPEC); C: follow-up and**

surveillance; O: prognostic effectiveness; S: randomized controlled trials.

Condition being studied: Appendiceal mucinous neoplasms (AMNs) are rare tumors that account for less than 2% of appendectomies. The World Health Organization classifies the majority of noninvasive epithelial lesions as low-grade appendiceal mucinous neoplasms (LAMNs). Histologically, LAMNs are characterized by well-differentiated adenomas that can proliferate outside the appendix in a biological malignant fashion. LAMNs may perforate and spread throughout the peritoneal cavity resulting in the distinctive and frequently aggressive syndrome called pseudomyxoma peritonei (PMP). Due to high relapse risk and unsatisfactory 10-year overall survival (OS) rate after treatment, PMP should be also regarded as malignancy. It is suggested that performing right hemicolectomy confers minimal survival benefit and is reserved for certain cases such as positive resection margins and lymph nodes after appendectomy or perforated appendix. Conversely, some medical centers advocate aggressive treatment approaches with prophylactic hyperthermic intraperitoneal chemotherapy (HIPEC) as an effective means to prevent development into widespread PMP. Thus, the aim of our meta-analysis is to investigate the comparative effectiveness and safety of enrolled prophylactic HIPEC regimens in patients with LAMNs after resection surgery. The results are expected to provide new evidences for more detailed individualized therapies for LAMNs.

METHODS

Search strategy: The search strategy of PubMed will be as follows: #1 ((((((appendiceal mucinous neoplasm) OR appendiceal mucinous tumor) OR appendiceal mucinous cystadenoma) OR appendiceal neoplasia) OR appendiceal cancer) OR appendicular tumor) OR appendix tumors #2 ((((intraperitoneal perfusion) OR "peritoneal perfusion") OR hyperthermic intraperitoneal chemotherapy) OR "heated intraperitoneal chemotherapy") intraperitoneal chemotherapy #3 (((((((("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]) #4 #1 AND #2 AND #3 This search strategy will be modified to be suitable for other certain electronic databases.

Participant or population: This study focuses on the patients with histopathologically confirmed low-grade appendiceal mucinous neoplasm (LAMN) after appendectomy or right colectomy and no peritoneal involvement. The surgical decision might be made according to the diagnosis of acute appendicitis or abnormal appendix seen during colonoscopy or unrelated operation. The operation might be conducted under the condition of open or laparoscopy.

Intervention: The prophylactic hyperthermic intraperitoneal chemotherapy (HIPEC) after resection surgery would be administrated as soon as the histopathologic diagnosis was established.

Comparator: Postoperative follow-up and surveillance.

Study designs to be included: RCTs.

Eligibility criteria: 1) Patients with histopathologically confirmed low-grade appendiceal mucinous neoplasm (LAMN) after appendectomy or right colectomy and no peritoneal involvement in the eligible studies; 2) Patients were randomly assigned into HIPEC or the control group in the eligible studies; 3) Long-term oncologic outcomes, including OS and DFS, were assessed in the eligible studies; 4) Available full text with complete data in English; 5) Sufficient data to extract hazard ratios (HRs), odds ratios (ORs) and respective 95% confidence intervals (CIs).

Information sources: A systematic search of MEDLINE, EMBASE, PubMed, Web of

science, and the Cochrane Library databases will be performed. The Cochrane Central Register of Controlled Trials, International Clinical Trials Registry Platform (ICTRP), clinicaltrials.gov and controlledtrials.com will be also searched for ongoing trials. The relative references, academic conferences and network resources in the included literature will be further screened for potential eligible ones. When multiple reports describing the same sample were published, the most recent or complete report will be included. All RCTs published in electronic databases before July 20, 2020 with language restricted in English will be included in this review study.

Main outcome(s): The primary outcomes are overall survival (OS) and disease-free survival (DFS). OS is defined as the time from randomization until death from any cause. DFS is defined as the time from randomization until recurrence, metastasis, or occurrence of pseudomyxoma peritonei (PMP) confirmed by imaging, laparoscopic exploration and biopsy.

Additional outcome(s): 1) peritonitis and sepsis; 2) colonic fistula; 3) chemotherapy-associated adverse events; 4) adhesive intestinal obstruction.

Data management: EndNote X9 software (Clarivate Analytics) will be employed to manage all citations, as well as for duplicates screening.

Quality assessment / Risk of bias analysis: The methodological quality of included studies will be evaluated by two reviewers using the Review Manager software version 5.3 (RevMan 5.3) '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 will be calculated in accordance with the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions and be graded into 3 levels, including 'High Risk', 'Low Risk', and 'Unclear'. Disagreements between two independent reviewers will be solved by discussion and consulting the expert in Evidence-Based Medicine (EBM). The RoB table and graph will be also drawn by RevMan 5.3.

Strategy of data synthesis: The RevMan 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) will be employed for statistical analysis. Continuous outcomes (OS, DFS) will be expressed as the hazard ratios (HRs) and relative 95% confidence intervals (CIs). Dichotomous outcomes (peritonitis and sepsis, colonic fistula, chemotherapy-associated adverse events, adhesive intestinal obstruction) will be expressed as the odds ratios (ORs) with 95% CIs. Statistical significance will be set at p.

Subgroup analysis: Subgroup analyses will be performed to explore possible sources of heterogeneity. Subgroup analyses will be conducted on the basis of sex, age, region, history of colorectal cancer, selective or emergency surgery, and appendectomy or extended resection surgery.

Sensibility analysis: The sensitivity analysis will be performed to ensure the stability of measure effects of primary outcomes by removing one by one those studies with 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 primary outcomes identified by sensitivity 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: appendiceal mucinous neoplasm; hyperthermic intraperitoneal chemotherapy; effectiveness; network meta-analysis; RCT.

Contributions of each author:
Author 1 - Wenming Yang - The author designed the research, identified the

feasibility of the study, and drafted the manuscript.

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

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 - Jikui Peng - 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.