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Endoscopic resection for non-polypoid dysplasia in inflammatory bowel disease: a systematic review protocol

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ABSTRACT

Introduction Non-polypoid low-grade dysplasia in inflammatory bowel disease is associated with a medium increased risk of colorectal cancer, while treatment recommendations remain controversial. We aim to evaluate the efficacy and safety of endoscopic treatment for non-polypoid dysplasia in patients with inflammatory bowel disease.

Methods and analysis Medline, Embase, Cochrane Library, Scopus, Web of Science and clinical trials registry from database inception to the search date will be used to retrieve eligible studies. Studies that report the curative resection rate or any of other secondary outcomes of endoscopic treatment in patients with non-polypoid dysplasia in inflammatory bowel disease will be included in the analysis. We will conduct quantitative synthesis if the eligible studies are homogeneous judging from clinical and methodological perspectives.

Ethics and dissemination Ethical approval for this study was waived by the Ethics Committee of Peking Union Medical College Hospital because there are no individual data involved in the analysis and all the combined results will be retrieved from study-level data. We plan to disseminate results through peer-reviewed journals or conference abstracts.

PROSPERO registration number CRD42019120413.

Strengths and limitations of this study

- The planned quantitative synthesis addressing endoscopic resection for non-polypoid in inflammatory bowel disease will overcome the limited statistical power in previous original studies.
- There is no restriction on population, study design or publication characteristics, providing an overall evidence map for clinical practice.
- Limited evidence from randomised controlled trials may weaken the confidence of the study conclusion.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic relapsing disease including ulcerative colitis (UC) and Crohn's disease (CD). The annual incidence of IBD is 37.0–39.4/100 000 person-years in Western countries and 11.3/10 000 person-years in the Asian area.[1] Patients with long-term IBD have an increased risk of colorectal cancer (CRC), and most cases of CRC are believed to arise from dysplasia.[2] Here, dysplasia refers to an unequivocal neoplastic alteration of the colonic epithelium without evidence of tissue invasion, which is characterised by specific cytological and/or architectural changes to the epithelium, and CRC refers to lesions that show histological evidence of invasion through the muscularis mucosa into the submucosa.[3] Besides, colitis-associated dysplasia should be distinguished from sporadic neoplasm by comprehensive judgement based on the site, morphology and histological feature of the lesion according to the European consensus.[4] The cumulative incidence of neoplasia (sporadic adenoma, UC-associated dysplasia and CRC) in patients with long-standing UC was 4.1% at 10 years, 14.1% at 20 years, 28.0% at 30 years and 38.9% at 40 years, with a CRC risk of 0.1%, 2.9%, 6.7% and 10.0%, respectively.[5] The HR of developing CRC in IBD patients with dysplasia compared with IBD patients without dysplasia was 7.8 for low-grade dysplasia (LGD) and 33.1 for high-grade dysplasia (HGD).[5] Therefore, timely surveillance and early treatment of precancerous lesions (dysplasia) are essential to prevent CRC in IBD.

The Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients International Consensus Recommendations (SCENIC) consensus classified IBD-dysplasia into visible and non-visible lesions, with visible lesions further divided into polypoid dysplasia (protruding from the mucosa into the lumen ≥2.5 mm) and non-polypoid dysplasia (<2.5 mm or no protrusion above the mucosa).[6] There is a strong association between HGD and CRC (synchronous[7] or metachronous[5]), justifying colectomy as a reasonable treatment for patients with IBD-HGD. With regard to LGD, polypoid LGD is believed to be an indication

for endoscopic resection, due to technical feasibility and much lower risk of recurrence. Treatment recommendations for non-polypoid LGD, however, remain controversial,[8] since non-polypoid LGD is associated with a medium risk (eg, between polypoid LGD[9] and HGD[5]) to develop CRC,[10] but requires much higher endoscopic skill to resect it.

Endoscopic resection techniques for non-polypoid LGD consist of endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). The safety of endoscopic resection for polypoid LGD has been confirmed by meta-analysis with a postoperative CRC risk of as low as 5/1000 person-years.[9] Data on CRC risk after resection of non-polypoid dysplasia in IBD are scarce. Submucosal fibrosis and the obscure margin of non-polypoid dysplasia in IBD are responsible for the technical difficulties in endoscopic resection.[11] With the development of endoscopic techniques, several studies started to fill the gap on endoscopic resection in the management of non-polypoid dysplasia.[12]

The small sample sizes and heterogeneity of these studies compromised the reliability of their conclusions. Therefore, it is crucial to perform a systematic review collecting and evaluating available studies and to establish a body of evidence for IBD patients with non-polypoid dysplasia undergoing endoscopic resection.

Objectives

This research protocol aims to evaluate the efficacy (curative resection rate, for example) and safety (such as recurrence, bleeding and perforation) of endoscopic treatment for non-polypoid dysplasia in patients with IBD.

METHODS AND ANALYSIS

The protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website and reported in compliance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement.[13] Any further amendments in the protocol and conduct of this systematic review will be recorded and submitted to the PROSPERO website and reported in future publications.

Inclusion criteria for study selection

Types of studies

Eligible studies may include retrospective or prospective cohort studies (single-arm or multiple exposure groups), consecutive case series, cross-sectional studies, or randomised controlled trials that reported at least one of the primary outcomes (curative resection rate) and secondary outcomes (en-bloc resection rate, CRC incidence rate, local recurrence rate, metachronous recurrence rate, rate of postoperative bleeding and perforation during the procedure, rate of submucosal fibrosis, and overall survival).

Types of participants

Patients diagnosed with IBD and non-polypoid dysplasia should be confirmed by clinical, endoscopic and histological evaluation. Here, dysplasia refers to an unequivocal neoplastic alteration of the colonic epithelium without evidence of tissue invasion, which is characterised by specific cytological and/or architectural changes to the epithelium.[3] Due to the update of terminology,[6] the term non-polypoid dysplasia here includes flat dysplasia, Paris 0-II lesions and laterally spreading tumours (lesions reach a large (>10 mm) lateral diameter without increasing their height or protrusion above the mucosa).[6 14] To avoid missing eligible studies, we will carefully check the definition of dysplasia-associated lesion or mass (DALM) and will only include those that fulfil the criteria for non-polypoid dysplasia, since the term DALM is confusing and is used to describe all irregular, diffuse masses or plaque lesions in actively or previously inflamed areas of the colon.

Types of interventions

Endoscopic resection includes EMR and ESD for non-polypoid dysplasia in IBD.

Types of outcome measures

The primary outcome in our systematic review is curative resection rate (R0 resection with submucosal invasion < 1000 mm, absent lymphovascular involvement) of non-polypoid dysplasia.[15] The secondary outcomes in this systematic review include en-bloc resection rate, R0 resection rate (en-bloc resection with negative horizontal and vertical margin), CRC incidence rate, local recurrence rate, metachronous recurrence rate, rate of postoperative bleeding and perforation during the procedure, rate of submucosal fibrosis, and overall survival.

Literature search for identification of studies

Potentially relevant studies will be searched using Medline, Embase, Cochrane Controlled Register of Trials, Scopus, Web of Science and ClinicalTrials.gov registry from database inception up to 1 July 2019. Free text and medical subject heading terms relevant to endoscopy, inflammatory bowel disease and dysplasia will be used in the literature search. We will not use any filter for study design. Hand search of the bibliographies of relevant review and systematic review articles will be also conducted. We will set no language limitation in the literature search. The detailed literature search strategy is shown in online supplementary table S1.

Data collection and analysis

Selection of studies

Records retrieved from the literature search will be imported into EndNote, and duplicate citations will be removed. Two investigators (WC and YZ) will independently assess the eligibility of the studies by reading the title and the abstract, and the full texts of potentially eligible studies will be used to determine the final eligibility. Disagreement during the literature screening and

inclusion process will be resolved by discussion with a methodologist (YLZ) and a gastroenterologist (DW). In each stage, we will record reasons for excluding citation in the EndNote library.

Data extraction and management

Data will be extracted into an Excel extraction form by one investigator (WC) and double-checked by one methodologist (YLZ). We will retrieve the following information from each eligible study:

- Basic information of the study: author, publication year, design and sample size.
- Patient characteristics: age, sex, duration of disease, inflammatory endoscopic/histological activity, lesion size, lesion location, submucosal fibrosis, different types of IBD (UC and CD) and primary sclerosing cholangitis.
- Detailed information on the endoscopic equipment for surveillance and techniques for therapy: white-light endoscopy (WLE), chromoendoscopy (CE), narrow band imaging (NBI), endoscopic mucosal resection (EMR), endoscopic submucosal disection (ESD) and so on.
- Outcome data: number of patients with en-bloc/R0/curative resection, postoperative bleeding and perforation, submucosal fibrosis, CRC incidence, local recurrence, metachronous recurrence, and overall survival in long-term follow-up.

We will make the most extensive use of all the available materials of the relevant studies, including but not limited to the publications, unpublished reports, information from study registries and online appendices. If the vital information is unavailable in the above sources, we will try to contact the investigators to get the relevant data through email. We will transform all the extracted data into the international system of units.

Risk of bias assessment

If relevant evidence is available, we will use the Cochrane Collaboration's tool to assess the risk of bias in randomised controlled trials and the Newcastle-Ottawa Scale to evaluate the risk of bias in two-armed cohort studies. For single-arm cohort studies, we will use a modified tool to assess the risk of bias of eligible studies based on the Agency for Healthcare Research and Quality (AHRQ) tool.[16] The risk of bias will be evaluated by one investigator (WC) and double-checked by one methodologist (YLZ). Any disagreement will be resolved by discussion with a senior investigator (DW). Detailed criteria of the modified AHRQ tool are shown in online supplementary table S2.

Statistical analysis

We will first describe the basic characteristics and the risk of bias of eligible studies. If eligible studies are in different designs, they will be reported and synthesised separately. We will assess the eligible studies in terms of heterogeneity by evaluating the clinical and methodological differences qualitatively, and if there is significant heterogeneity quantitative synthesis will be abandoned.

This planned systematic review aims to collect evidence from randomised clinical trials and observational studies. However, we anticipate that the data on outcomes of interest will be mostly reported in single-arm cohort studies, lacking comparison between randomly allocated intervention groups. Considering the potential clinical and methodological heterogeneity among eligible observational studies, we will use a random-effects model to combine the effect.[17] The curative resection rate and all the secondary outcomes with 95% CI will be pooled as proportion with logit transformation if there are enough data supporting the synthesis.[18] Clopper-Pearson interval method will serve to estimate the 95% CI in each study.[19]

Between-study variance will be estimated using the restricted maximum likelihood estimator.[20] We will measure heterogeneity between studies using I^2 statistics, and an I^2 value larger than 50% will be defined as substantial heterogeneity.[21]

We do not plan to assess reporting bias in this systematic review since the hypothesis behind the commonly applied methods for detecting reporting bias may not apply to single-arm rates or proportions.[22]

Subgroup analysis will be conducted with regard to lesion size, lesion location, duration of the disease, submucosal fibrosis and different types of IBD (UC and CD). We will perform post-hoc subgroup analysis if there is evidence that some crucial sources contribute to the statistical heterogeneity. The potential sources of heterogeneity will be further assessed using multiple random-effects meta-regression to explore the independent contribution of each variable to the main outcome. Results from post-hoc subgroup analysis will be interpreted as hypothesis-generating rather than definite evidence for subgroup difference.

Sensitivity analysis using different transformation methods (log transformation, Freeman-Tukey double arcsine transformation, arcsine transformation or raw proportion without transformation) will be conducted to check if the main findings are robust. All statistical analyses will be completed in R V.3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) with a two-sided α of 0.05.

Grading the quality of evidence

The quality of evidence for all the outcomes will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group methodology.[23] Detailed evaluation methods will follow the recommendations from GRADE working group.

Patient and public involvement

Patients or the public are not involved in the design and conception of this study.

Ethics and dissemination

This is a research protocol for a systematic review and the data are not collected yet; hence, there are no data published in a data repository. The results will be disseminated through peer-reviewed publications or conference abstracts.

DISCUSSION

Indefinite margins and submucosal fibrosis add to the technical difficulties for endoscopic resection of non-polypoid dysplasia. Our meta-analysis will evaluate the overall en-bloc/R0/curative resection rate and implement subgroup analysis according to potential influencing factors such as lesion size and inflammatory activity to select patients who may benefit most from endoscopic therapy. Given that the incidence of metachronous dysplasia and CRC remains largely unknown in non-polypoid dysplasia after endoscopic resection,[6] this planned systematic review and meta-analysis will provide useful information on long-term prognosis. We will also compare our results with the evidence from polypoid dysplasia which was cited by ECCO[8] and SCENIC[6] guidelines, which may help clinicians make reasonable therapeutic strategies for the management of non-polypoid dysplasia in IBD. Besides, endoscopic resection has the advantage of less complication risk and patient preference[24]; therefore, if endoscopic resection proves reasonably effective and safe for the management of non-polypoid dysplasia, it may become the first-choice therapy in such patients. However, this systematic review have some potential limitations. The best evidence evaluating the effect of endoscopic resection should come from randomised controlled trials comparing endoscopic resection versus other therapies in patients with non-polypoid dysplasia in IBD. However, based on our pilot literature search, few studies, if any, have addressed this problem in a randomised design. The data synthesis from single-arm cohort studies or other relevant data sources may be highly sensitive to the selection of population and the practice setting. Hence, we are justified to expect significant heterogeneity across studies. Moreover, the potentially limited follow-up periods may be insufficient to observe long-term outcome events such as CRC incidence, local recurrence and overall survival. The underlying heterogeneity regarding clinical and methodological considerations should be evaluated using subgroup analysis or meta-regression. Nevertheless, the number of eligible studies is expected to be small, given the relatively late application of endoscopic techniques in practice, limiting our ability to analyse influencing factors for treatment effectiveness.

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Contributors DW is the guarantor of this systematic review and launched this research. WC and YZ completed the pilot literature search and will conduct the formal literature search and screening. YLZ designed the data extraction form, the tool for risk of bias assessment and the data synthesis plan. WC and YZ will extract the data. YLZ will conduct the quantitative synthesis. DW, WC, YZ and YLZ will interpret the results. All the authors contributed to the drafting of the manuscript and approved the publication.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Formal ethical approval is waivered since there are no individual data involved in the analysis and all the combined results will be retrieved from study-level data.

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