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

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TITLE

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

AUTHORSHIP

Yue-Lun Zhang, PhD[1, 2]*, Wei Chen[2]*, Yi Zhao[2], Dong Wu, MD[2].

1 Department of Gastroenterology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College

2 Central Research Laboratory, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College

*These authors contributed equally and should be regarded as co-first authors.

Corresponding to Dr. Wu, Dong (wudong061002@aliyun.com, Department of Gastroenterology, Peking Union Medical College Hospital, 1 Shuaifuyuan, Dongcheng District, Beijing, China, 100730).

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ABSTRACT

Introduction

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

Methods and analysis

Medline, Embase, Cochrane Library, and clinical trials registry from database inception to the search date will be used to retrieve the 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 patients with non-polypoid dysplasia in inflammatory bowel disease will be included in the analysis. Quantitative synthesis will be conducted if the eligible studies are homogeneous judging from clinical and methodological perspective.

Ethics and dissemination

A formal ethical approval is waivered since there is no individual data involved in the analysis and all the combined results will be retrieved from study-level data. The results will be disseminated through peer-reviewed journals or conference abstracts.

Registration number

CRD42019120413.

Key words

Non-polypoid dysplasia, inflammatory bowel diseases, endoscopy, systematic review, protocol.

INTRODUCTION

Description of the condition

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 11.3/10000 person-years in 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] The cumulative incidence of neoplasia (sporadic adenoma, dysplasia, and CRC) in long-standing UC patients was 4.1% at 10 years, 14.1% at 20 years, 28% at 30 years, and 38.9% at 40 years, with CRC risk of 0.1%, 2.9%, 6.7%, 10.0%, respectively.[3] The hazard ratio of developing CRC in IBD patients with dysplasia compared to IBD patients without dysplasia was 7.8 for low grade dysplasia (LGD) and 33.1 for high grade dysplasia (HGD).[3] Therefore, timely surveillance and early treatment of precancerous lesions (dysplasia) are essential to prevent CRC in IBD.

According to the SCENIC consensus, IBD-dysplasia is classified into visible and non-visible. And visible lesions are further divided into polypoid dysplasia (PD, protruding from the mucosa into the lumen $\geqslant$ 2.5 mm) and non-polypoid dysplasia (NPD, $<$ 2.5 mm or no protrusion above the mucosa) dysplasia.[4] There is a strong association between high-grade dysplasia (HGD) and synchronous[5] or metachronous[3] CRC, justifying colectomy as a reasonable treatment for patients with IBD-HGD. With regards to low-grade dysplasia (LGD), polypoid LGD (PLGD) 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 (NPLGD), however, remain controversial,[6] since NPLGD has medium risk (e.g., between PLGD[8] and HGD[3]) to develop CRC[7] but requires much higher endoscopic skill to resect it.

Description of the intervention

Endoscopic resection techniques for NPLGD consist of endoscopic mucosal resection

(EMR) and endoscopic submucosal dissection (ESD). The safety of endoscopic resection for PLGD has been well confirmed by meta-analysis with post-operation CRC risk of as low as 5/1000 pearson-years.[8] Data about cancer risk after resection of NPD in IBD are scarce. The submucosal fibrosis and obscure margin of NPD in IBD are responsible for technical difficulties in endoscopic resection.[9] With the development of endoscopic techniques, several studies started to fill the gap in the literature on endoscopic resection in the management of NPD.[10]

Why it is important to do this review

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

Objectives

This systematic review and meta-analysis aims to evaluate effectiveness (curative resection rate, etc.) and safety (recurrence, bleeding, perforation, etc.) of endoscopic treatment for the non-polypoid dysplasia in patients with inflammatory bowel disease.

METHODS AND ANALYSIS

The protocol was registered on the PROSPERO website (CRD42019120413) and reported in compliance with PRISMA-P statement.[11] Any further amendments in the protocol and conducting of this systematic review will be recorded and submitted to the PROSPERO website and reported in the 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 randomized controlled trials that reporting at least one of the primary outcomes

(curative resection rate) and secondary outcomes (en-bloc resection rate, incidence of carcinogenesis, 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 inflammatory bowel disease and non-polypoid dysplasia confirmed by clinical, endoscopic and histological evaluation. Due to the update of terminology, the term non-polypoid dysplasia here includes flat dysplasia, Paris 0-II lesions, and laterally spreading tumors.[4]

Types of interventions

The 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 of non-polypoid dysplasia.[12] The secondary outcomes in this systematic review include en-bloc resection rate, complete resection rate, incidence of carcinogenesis, local recurrence rate, metachronous recurrence rate, rate of postoperative bleeding and perforation during the procedure, rate of submucosal fibrosis, and overall survival.

Search methods for identification of studies

Potentially relevant studies will be searched using Medline, Embase, the Cochrane Controlled Register of Trials (CENTRAL), and clinicaltrials.gov registry from database inception up to 1 February 2019. Free text and MeSH terms relevant with endoscopy, inflammatory bowel disease, and dysplasia will be used in the literature search. No filter for study design will be used. Hand search of the bibliographies of relevant review and systematic review articles will be also conducted. There is no language limitation in the literature search. Detailed literature search strategy is shown in Supplemental Table S1.

Data collection and analysis

Selection of studies

Records retrieved from literature search will be imported into Endnote and duplicated citations will be removed. Two investigators (CW and ZY) will independently assess the eligibility of the citations using the title and abstract and full texts of potentially eligible studies will be used to judge the final eligibility. Disagreement during the literature screening and inclusion will be resolved by discussion with a methodologist (ZYL). Reasons for excluding citations in each stage will be noted in Endnote library.

Data extraction and management

Data will be extracted into an Excel extraction form by one investigator (CW) and double-checked by one methodologist (ZYL). The following information will be extracted from each eligible study: 1) basic information of the study (author, publication year, design); 2) patients' characteristics (age, sex, duration of disease, lesion size, lesion location, submucosal fibrosis and different types of IBD (UC and CD)); 3) detailed information of the endoscopic therapy (EMR, ESD, etc.); 4) outcome data (total number of patients receiving the endoscopic resection for non-polypoid dysplasia, number of patients with en-bloc/complete/curative resection, postoperative bleeding and perforation, submucosal fibrosis, carcinogenesis, local recurrence, and metachronous recurrence, and overall survival in long-term follow-up). We will make the largest use of all the available materials of the relevant studies, including but not limited to the publication for the main results and study design, unpublished report, information from study registry, and online appendices. If the key information was not reported in the above sources, we will try to contact the investigators to get the relevant data through email.

Risk of bias assessment

This planned systematic review aims to collect evidence from randomized clinical trials and observational studies. The current available tools for the risk of bias assessment need to be modified to assess the risk of bias of eligible studies, since we anticipate that

the data of resection rate will be mostly reported in single-arm cohort studies, lacking comparison between different intervention groups that could be addressed by commonly used tools such as the Newcastle-Ottawa Scale (NOS). Thus 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.[13] Selection bias, performance bias, attrition bias, detection bias, and reporting bias will evaluated by one investigator (CW) and double checked by one methodologist (ZYL). Any disagreement will be resolved by discussion with a senior investigator (WD). Detailed criteria to assess the risk of bias are shown in Supplemental Table S2. Results from risk of bias assessment will be tabulated shown.

Statistical analysis

We will firstly describe the basic characteristics and risk of bias of eligible studies. If studies with different designs were eligible, they will be reported and synthesized separately. The eligible studies will be assessed in terms of heterogeneity by evaluating the clinical and methodological differences qualitatively, and if there was significant heterogeneity, quantitative synthesis will be abandoned. Considering the potential heterogeneity among eligible studies, random-effects model will be used to combine the effect. The curative resection rate and other secondary outcomes with 95% CI will be pooled as proportion with logit transformation. Clopper-Pearson interval method will be used to estimate the CI in each individual study. The between-study variance will be estimated using the restricted maximum-likelihood estimator. We will measure heterogeneity between studies using I^2 statistics and we will not use predefined criteria of I^2 statistics for significant heterogeneity. There is no planned assessment for reporting bias in this systematic review since the hypothesis behind the commonly applied methods for detecting reporting bias may not be satisfied in the meta-analysis for single-armed rate or proportions.

Subgroup analysis will be conducted with regards to lesion size, lesion location, duration of the disease, submucosal fibrosis and different types of IBD (UC and CD).

Post-hoc subgroup analysis will be conducted if there is evidence that some important 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 the statistical analysis will be completed in R (version 3.5.2) with 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.[14] Detailed evaluation methods will follow the recommendations from GRADE working group.

Role of funding source, ethics, conflict of interest, and dissemination

This systematic review and meta-analysis is funded by Peking Union Medical College (100232017). The sponsor has no role in study design, data collection, data analysis, and results interpretation. A formal ethical approval is waivered since there is no individual data involved in the analysis and all the combined results will be retrieved from study-level data. This is a research protocol for a systematic review and the data are not collected yet, hence, there is no data published in a data repository. All the authors declared that there was no conflict of interest. The results will be disseminated through peer-reviewed publications or conference abstracts.

DISCUSSION

Taking into account the lack of evidence in natural history for non-polypoid dysplastic

lesions after endoscopic resection,[4] this planned systematic review and meta-analysis will provide useful information leading to reasonable therapeutic strategies for management of non-polypoid dysplasia in IBD. This systematic review may have some potential limitations. The best evidence evaluating the effect of endoscopic resection should come from randomized controlled trials comparing the endoscopic resection versus other therapies in patients with non-polypoid dysplasia in inflammatory bowel disease. However, based on our pilot literature search, few studies, if any, have addressed this problem in a randomized design. The data synthesis from a single-arm cohort studies or other relevant data sources may be highly sensitive to the selection of population, hence, there may be significant heterogeneity between studies.

CONTRIBUTION

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

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ARTICLE SUMMARY

Strengths and limitations of this study

The systematic review will evaluate the current available evidence of the treatment effectiveness of endoscopic resection for non-polypoid in inflammatory bowel disease.

There is no restriction on population, study design, or publication characteristics (e.g. language).

The planned quantitative synthesis will overcome the limited statistical power in the previous original studies.

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FIGURES AND TABLES

Table. Literature search strategy in Medline.

#	Term
1	Exp Inflammatory bowel disease/
2	Crohn*.mp.
3	Ulcerative colitis*.mp
4	IBD.mp.
5	Inflammatory bowel disease*.mp.
6	OR/1-5
7	Exp Colonic Neoplasms/
8	(dysplas* OR neoplas* OR adenom* OR polyp*).mp.
9	DALM.mp.
10	colit* AND associat* AND (lesion* OR mass*).mp.
11	OR/7-10
12	6 AND 11
13	exp Endoscopic Mucosal Resection/
14	(endoscop* AND (therap* OR dissect* OR resect* OR treat*)).mp./ (endoscop* ADJ5 (therap* OR dissect* OR resect* OR treat*)).mp.
15	(ESD OR EMR OR EPMR OR ER).mp.
16	OR/13-15
17	12 AND 16

ONLINE ONLY APPENDICES

Supplemental Table. Criteria for risk of bias assessment of eligible studies.

Domain	Item	Response
Selection bias	Did the study apply clear inclusion/exclusion criteria in the selection of participants?	Low risk, the study reported clear and appropriate inclusion/exclusion criteria; high risk, the criteria used in the study may lead to bias in the estimation of the curative resection rate; unclear, there is no relevant information.
	Were the participants representative of the targeted population?	Low risk, the participants were recruited consecutively or using probability sampling method; high risk, the participants in the study were biased from the targeted population; unclear, there is no relevant information.
Performance bias	Did researchers rule out any impact from a concurrent intervention or an unintended exposure	Low risk, there was no concurrent or unintended intervention, or the existing concurrent intervention is unlikely to influence the resection rate; high risk, there were some concurrent or unintended intervention that may influence the resection rate; unclear, there is no relevant information.

Domain	Item	Response
	that might bias results?	
	Did variation from the study protocol compromise the conclusions of the study?	Low risk, the reporting results are concordant with the information from registration and study protocol; high risk, there are some changes in the conducting of the study compared with the registration or study protocol; unclear, there is no available registration or protocol.
Attrition bias	Was the follow-up completed in all subjects?	Low risk, the primary outcome (curative resection) could be assessed in more than or equal to 90% of the participants, or there is solid evidence indicating that those who lose to follow-up were similar with those still staying in the cohort; high risk, less than 90% of the participants contributed to the primary outcome; or there is evidence indicating that those who lose to follow-up were different with those still staying in the cohort; unclear, there is no relevant information.
Detection bias	Were the outcome assessors blinded to the intervention or exposure status of participants?	Low risk, the outcome assessor were totally blinded to the intervention; high risk, the outcome assessor knew the intervention; unclear, there is no relevant information.

Domain	Item	Response
	Were the inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?	Low risk, the personnel who recruited the participants were unaware of the intervention, or objective measures were used in the patients recruiting; high risk, the personnel who recruited the participants were aware of the intervention, or there is evidence that the recruiting of participants will lead to biased estimation of the primary outcome; unclear, there is no relevant information.
	Were primary outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Low risk, the personnel who assessed the outcome were unaware of the intervention, or objective measures were used in the primary outcome; high risk, the personnel who assessed the outcome were aware of the intervention, or there is evidence that the assessment of the primary outcome will lead to biased estimation; unclear, there is no relevant information.
Reporting bias	Were the potential	Low risk, all the predefined outcomes in registration or study protocol were reported in the

Domain	Item	Response
	outcomes pre-specified by the researchers? Are all pre-specified outcomes reported?	study; high risk, the investigators selectively reported some predefined outcomes, or there are changes in the outcomes of interest; unclear, there is no available registration or study protocol.

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	Page 1.
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a. This is not an update of a previous review.

	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2.
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1.
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 7.
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Page 2.
Sources	#5a	Indicate sources of financial or other support for the review	Page 6.
Sponsor	#5b	Provide name for the review funder and / or sponsor	Page 6.
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	Page 6.
Rationale	#6	Describe the rationale for the review in the context of what is already known	Page 1 to 2.
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 2.
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study	Page 2 to 3.

		design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 3.
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 3 and 9.
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 4.
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 4.
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 4.
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 4.

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 3.
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 4 and 5.
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	Page 5.
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	Page 5.
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 5 and 6.
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 5.
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 5.
Confidence in cumulative	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 6.

evidence

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Yue-Lun Zhang, PhD[1, 2]*, Wei Chen[2]*, Yi Zhao[2], Dong Wu, MD[2].

1 Department of Gastroenterology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College

2 Central Research Laboratory, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College

*These authors contributed equally and should be regarded as co-first authors.

Corresponding to Dr. Wu, Dong (wudong061002@aliyun.com, Department of Gastroenterology, Peking Union Medical College Hospital, 1 Shuaifuyuan, Dongcheng District, Beijing, China, 100730).

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ABSTRACT

Introduction

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

Methods and analysis

Medline, Embase, Cochrane Library, the Scopus, Web of Science, and clinical trials registry from database inception to the search date will be used to retrieve the 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 patients with non-polypoid dysplasia in inflammatory bowel disease will be included in the analysis. Quantitative synthesis will be conducted if the eligible studies are homogeneous judging from clinical and methodological perspective.

Ethics and dissemination

A formal ethical approval is waivered since there is no individual data involved in the analysis and all the combined results will be retrieved from study-level data. The results will be disseminated through peer-reviewed journals or conference abstracts.

Registration number

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Key words

Non-polypoid dysplasia, inflammatory bowel diseases, endoscopy, systematic review, protocol.

Strengths and limitations of this study

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

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 11.3/10000 person-years in 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] The cumulative incidence of neoplasia (sporadic adenoma, UC associated dysplasia, and CRC) in long-standing UC patients was 4.1% at 10 years, 14.1% at 20 years, 28% at 30 years, and 38.9% at 40 years, with CRC risk of 0.1%, 2.9%, 6.7%, 10.0%, respectively.[3] The hazard ratio of developing CRC in IBD patients with dysplasia compared to IBD patients without dysplasia was 7.8 for low grade dysplasia (LGD) and 33.1 for high grade dysplasia (HGD).[3] Therefore, timely surveillance and early treatment of precancerous lesions (dysplasia) are essential to prevent CRC in IBD.

According to the SCENIC consensus, IBD-dysplasia is classified into visible and non-visible. And visible lesions are further divided into polypoid dysplasia (protruding from the mucosa into the lumen $\geqslant$ 2.5 mm) and non-polypoid dysplasia ($<$ 2.5 mm or no protrusion above the mucosa) dysplasia.[4] There is a strong association between HGD and synchronous[5] or metachronous[3] CRC, justifying colectomy as a reasonable treatment for patients with IBD-HGD. With regards 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,[6] since non-polypoid LGD has medium risk (e.g., between polypoid LGD[7] and HGD[3]) to develop CRC[8] 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 well confirmed by meta-analysis with

post-operation CRC risk of as low as 5/1000 person-years.[7] Data about cancer risk after resection of non-polypoid dysplasia in IBD are scarce. The submucosal fibrosis and obscure margin of non-polypoid dysplasia in IBD are responsible for technical difficulties in endoscopic resection.[9] With the development of endoscopic techniques, several studies started to fill the gap in the literature on endoscopic resection in the management of non-polypoid dysplasia.[10]

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

Objectives

This research protocol aims to report the methodology of a planned systematic review and meta-analysis that will evaluate the effectiveness (curative resection rate, etc.) and safety (recurrence, bleeding, perforation, etc.) of endoscopic treatment for the non-polypoid dysplasia in patients with inflammatory bowel disease.

METHODS AND ANALYSIS

The protocol was registered on the PROSPERO website (CRD42019120413) and reported in compliance with PRISMA-P statement.[11] Any further amendments in the protocol and conducting of this systematic review will be recorded and submitted to the PROSPERO website and reported in the 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 randomized 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 inflammatory bowel disease and non-polypoid dysplasia confirmed by clinical, endoscopic and histological evaluation. Here, dysplasia refers to an unequivocal neoplastic alteration of the colonic epithelium with the potential to become invasive, which is characterized by specific nuclear, cellular and architectural changes to the epithelium.[12] Due to the update of terminology,[4] the term non-polypoid dysplasia here includes flat dysplasia, Paris 0-II lesions, and laterally spreading tumors (lesions reach a large (>10 mm) lateral diameter without increasing their height or protrusion above the mucosa).[4,13] Besides, as the term DALM is confusing and also used to describe all irregular, diffuse masses or plaque lesions in actively or previously inflamed areas of the colon, to avoid missing eligible studies, we will carefully check the definition of DALM and will only include those that fulfill the criteria of non-polypoid dysplasia.

Types of interventions

The 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 of non-polypoid dysplasia.[14] The secondary outcomes in this systematic review include en-bloc resection rate, complete 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.

Search methods for identification of studies

Potentially relevant studies will be searched using Medline, Embase, the Cochrane Controlled Register of Trials (CENTRAL), the Scopus, Web of Science, and clinicaltrials.gov registry from database inception up to 1 July 2019. Free text and MeSH terms relevant with endoscopy, inflammatory bowel disease, and dysplasia will be used in the literature search. No filter for study design will be used. Hand search of the bibliographies of relevant review and systematic review articles will be also conducted. There is no language limitation in the literature search. Detailed literature search strategy is shown in Supplemental Table S1.

Data collection and analysis

Selection of studies

Records retrieved from literature search will be imported into Endnote and duplicated citations will be removed. Two investigators (CW and ZY) will independently assess the eligibility of the citations using the title and abstract and full texts of potentially eligible studies will be used to judge the final eligibility. Disagreement during the literature screening and inclusion will be resolved by discussion with a methodologist (ZYL). Reasons for excluding citations in each stage will be noted in Endnote library.

Data extraction and management

Data will be extracted into an Excel extraction form by one investigator (CW) and double-checked by one methodologist (ZYL). The following information will be extracted from each eligible study: 1) basic information of the study (author, publication year, design); 2) patients' characteristics (age, sex, duration of disease, inflammatory endoscopic/histological activity, lesion size, lesion location, submucosal fibrosis and different types of IBD (UC and CD), primitive sclerosing cholangitis (PSC)); 3) detailed information of the endoscopic equipments for surveillance and techniques for therapy (WLE, CE, NBI, EMR, ESD, etc.); 4) outcome data (total number of patients receiving the endoscopic resection for non-polypoid dysplasia, number of patients with

en-bloc/complete/curative resection (complete resection with submucosal invasion < 1000 mm, absent lymphovascular involvement, good cell differentiation), postoperative bleeding and perforation, submucosal fibrosis, CRC incidence, local recurrence, and metachronous recurrence, and overall survival in long-term follow-up). We will make the largest use of all the available materials of the relevant studies, including but not limited to the publication for the main results and study design, unpublished report, information from study registry, and online appendices. If the key information was not reported in the above sources, we will try to contact the investigators to get the relevant data through email. All the extracted data will be transformed into the International System of Units.

Risk of bias assessment

This planned systematic review aims to collect evidence from randomized clinical trials and observational studies. The current available tools for the risk of bias assessment need to be modified to assess the risk of bias of eligible studies, since we anticipate that the data of resection rate will be mostly reported in single-arm cohort studies, lacking comparison between different intervention groups that could be addressed by commonly used tools such as the Cochrane Collaboration's tool for assessing risk of bias in randomised controlled trials and the Newcastle-Ottawa Scale (NOS). If there were any evidence from traditional randomised studies or cohort studies, we will use the Cochrane Collaboration's tool and the NOS to evaluate the risk of bias. Otherwise, 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.[15] Selection bias, performance bias, attrition bias, detection bias, and reporting bias will evaluated by one investigator (CW) and double checked by one methodologist (ZYL). Any disagreement will be resolved by discussion with a senior investigator (WD). Detailed criteria to assess the risk of bias are shown in Supplemental Table S2. Results from risk of bias assessment will be tabulated shown.

Statistical analysis

We will firstly describe the basic characteristics and risk of bias of eligible studies. If studies with different designs were eligible, they will be reported and synthesized separately. The eligible studies will be assessed in terms of heterogeneity by evaluating the clinical and methodological differences qualitatively, and if there was significant heterogeneity, quantitative synthesis will be abandoned. Considering the potential clinical and methodological heterogeneity among eligible studies, random-effects model will be used to combine the effect. The curative resection rate and other secondary outcomes with 95% CI will be pooled as proportion with logit transformation.[16] Clopper-Pearson interval method will be used to estimate the CI in each individual study.[17] The between-study variance will be estimated using the restricted maximum-likelihood estimator.[18] We will measure heterogeneity between studies using I^2 statistics and we will not use predefined criteria of I^2 statistics for significant heterogeneity.[19,20] There is no planned assessment for reporting bias in this systematic review since the hypothesis behind the commonly applied methods for detecting reporting bias may not be satisfied in the meta-analysis for single-armed rate or proportions.[21]

Subgroup analysis will be conducted with regards to lesion size, lesion location, duration of the disease, submucosal fibrosis and different types of IBD (UC and CD). Post-hoc subgroup analysis will be conducted if there is evidence that some important 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 the statistical analysis will be completed in R (R Foundation for Statistical Computing, Vienna, Austria, version 3.5.2) with 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.[22] Detailed evaluation methods will follow the recommendations from GRADE working group.

Role of funding source, ethics, conflict of interest, and dissemination

This systematic review and meta-analysis is funded by Peking Union Medical College (100232017). The sponsor has no role in study design, data collection, data analysis, and results interpretation. A formal ethical approval is waivered since there is no individual data involved in the analysis and all the combined results will be retrieved from study-level data. This is a research protocol for a systematic review and the data are not collected yet, hence, there is no data published in a data repository. The results will be disseminated through peer-reviewed publications or conference abstracts.

Competing Interest statement

All the authors declared that there was no conflict of interest.

Patient and Public Involvement

Patients and or public are not involved.

DISCUSSION

There exist technical difficulties for endoscopic resection of non-polypoid dysplasia due to indefinite margin and submucosal fibrosis. Our meta-analysis will evaluate the overall en-bloc/complete/curative resection rate and implement subgroup analysis according to potential influence factors such as lesion size, inflammatory activity to

select patients who may benefit more from endoscopic therapy. In another aspect, taking into account the lack of evidence in natural history for non-polypoid dysplasia after endoscopic resection especially for metachronous dysplasia and CRC incidence rate,[4] this planned systematic review and meta-analysis will provide useful information of long-term prognosis. We will also compare our results with the evidence from polypoid dysplasia which was cited by ECCO[6] and SENIC[4] guidelines which may help to make reasonable therapeutic strategies for management of non-polypoid dysplasia in IBD. Besides, endoscopic resection has advantage for less complication risk and confirms to patients' preference,[23] therefore, if endoscopic resection is reasonable for management of non-polypoid dysplasia, it could be recommended as primary management. However, this systematic review may have some potential limitations. The best evidence evaluating the effect of endoscopic resection should come from randomized controlled trials comparing the endoscopic resection versus other therapies in patients with non-polypoid dysplasia in inflammatory bowel disease. However, based on our pilot literature search, few studies, if any, have addressed this problem in a randomized design. The data synthesis from a single-arm cohort studies or other relevant data sources may be highly sensitive to the selection of population and the practice setting, hence, there may be significant heterogeneity between studies. Moreover, the potential limited follow-up may be insufficient to observe enough cases for some long-term outcome events such as CRC incidence rate, local recurrence rate, and overall survival. The underlying heterogeneity regarding to clinical and methodological considerations should be evaluated using subgroup analysis or meta-regression. Nevertheless, the number of eligible studies are expected to be small given the relatively late application of this technique in practice, limiting our ability of analyzing the impact factor of the treatment effectiveness.

CONTRIBUTION

WD is the guarantor of this systematic review and launched this research. CW and ZY

completed the pilot literature search and will conducted the formal literature search and screening. ZYL designed the data extraction form, the tool for risk of bias assessment, and data synthesis plan. CW and ZY will extract the data. ZYL will conduct the quantitative synthesis. WD, CW, ZY, and ZYL will interpret the results. All the authors contributed to the drafting of the manuscript and approved the publication.

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Supplementary Table 1. Literature search strategy in Medline.

#	Term
1	Exp Inflammatory bowel disease/
2	Crohn*.mp.
3	Ulcerative colitis*.mp
4	IBD.mp.
5	Inflammatory bowel disease*.mp.
6	OR/1-5
7	Exp Colonic Neoplasms/
8	(dysplas* OR neoplas* OR adenom* OR polyp*).mp.
9	DALM.mp.
10	colit* AND associat* AND (lesion* OR mass*).mp.
11	OR/7-10
12	6 AND 11
13	exp Endoscopic Mucosal Resection/
14	(endoscop* AND (therap* OR dissect* OR resect* OR treat*)).mp./ (endoscop* ADJ5 (therap* OR dissect* OR resect* OR treat*)).mp.
15	(ESD OR EMR OR EPMR OR ER).mp.
16	OR/13-15
17	12 AND 16

Supplementary Table 2. Detailed criteria to assess the risk of bias.

Domain	Item	Response
Selection bias	1.Did the study apply clear inclusion/exclusion criteria in the selection of participants?	Low risk, the study reported clear and appropriate inclusion/exclusion criteria; high risk, the criteria used in the study may lead to bias in the estimation of the curative resection rate; unclear, there is no relevant information.
	2.Were the participants representative of the targeted population?	Low risk, the participants were recruited consecutively or using probability sampling method; high risk, the participants in the study were biased from the targeted population; unclear, there is no relevant information.
Performance bias	1.Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?	Low risk, there was no concurrent or unintended intervention, or the existing concurrent intervention is unlikely to influence the resection rate; high risk, there were some concurrent or unintended intervention that may influence the resection rate; unclear, there is no relevant information.
	2.Did variation from the study protocol	Low risk, the reporting results are concordant with the information from registration and study protocol; high risk, there are some changes in the conducting of the study compared with the

Domain	Item	Response
	compromise the conclusions of the study?	registration or study protocol; unclear, there is no available registration or protocol.
Attrition bias	1.Was the follow-up completed in all subjects?	Low risk, the primary outcome (curative resection) could be assessed in more than or equal to 90% of the participants, or there is solid evidence indicating that those who lose to follow-up were similar with those still staying in the cohort; high risk, less than 90% of the participants contributed to the primary outcome; or there is evidence indicating that those who lose to follow-up were different with those still staying in the cohort; unclear, there is no relevant information.
Detection bias	1.Were the outcome assessors blinded to the intervention or exposure status of participants?	Low risk, the outcome assessor were totally blinded to the intervention; high risk, the outcome assessor knew the intervention; unclear, there is no relevant information.

Domain	Item	Response
	2.Were the inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?	Low risk, the personnel who recruited the participants were unaware of the intervention, or objective measures were used in the patients recruiting; high risk, the personnel who recruited the participants were aware of the intervention, or there is evidence that the recruiting of participants will lead to biased estimation of the primary outcome; unclear, there is no relevant information.
	3.Were primary outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Low risk, the personnel who assessed the outcome were unaware of the intervention, or objective measures were used in the primary outcome; high risk, the personnel who assessed the outcome were aware of the intervention, or there is evidence that the assessment of the primary outcome will lead to biased estimation; unclear, there is no relevant information.
Reporting bias	1.Were the potential outcomes pre-specified by	Low risk, all the predefined outcomes in registration or study protocol were reported in the study; high risk, the investigators selectively reported some predefined outcomes, or there are

Domain	Item	Response
	the researchers? Are all pre-specified outcomes reported?	changes in the outcomes of interest; unclear, there is no available registration or study protocol.

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	Page 2.
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a. This is not an update of a previous review.

	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2.
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page.
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 8.
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Page 2.
Sources	#5a	Indicate sources of financial or other support for the review	Page i and 7.
Sponsor	#5b	Provide name for the review funder and / or sponsor	Page i and 7.
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	Page 7.
Rationale	#6	Describe the rationale for the review in the context of what is already known	Page 1 to 2.
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 2.
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study	Page 2 to 3.

		design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 3.
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 4.
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 4.
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 4.
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 4.
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 4.

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 3.
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 5.
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	Page 6.
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	Page 6.
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 6 and 7.
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 6.
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 6 and 7.
Confidence in cumulative	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 7.

evidence

BMJ Open

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

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TITLE

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

AUTHORSHIP

Yue-Lun Zhang, PhD[1, 2]*, Wei Chen[1]*, Yi Zhao[1], Dong Wu, MD[1].

1 Department of Gastroenterology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College

2 Central Research Laboratory, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College

*These authors contributed equally and should be regarded as co-first authors.

Corresponding to Dr. Wu, Dong (wudong061002@aliyun.com, Department of Gastroenterology, Peking Union Medical College Hospital, 1 Shuaifuyuan, Dongcheng District, Beijing, China, 100730).

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ABSTRACT

Introduction

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

Methods and analysis

Medline, Embase, Cochrane Library, the Scopus, Web of Science, and clinical trials registry from database inception to the search date will be used to retrieve the 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 patients with non-polypoid dysplasia in inflammatory bowel disease will be included in the analysis. Quantitative synthesis will be conducted if the eligible studies are homogeneous judging from clinical and methodological perspective.

Ethics and dissemination

A formal ethical approval is waivered since there is no individual data involved in the analysis and all the combined results will be retrieved from study-level data. The results will be disseminated through peer-reviewed journals or conference abstracts.

Registration number

CRD42019120413.

Key words

Non-polypoid dysplasia, inflammatory bowel diseases, endoscopy, systematic review, protocol.

Strengths and limitations of this study

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

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 11.3/10000 person-years in 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 characterized by specific cytological and/or architectural changes to the epithelium, and CRC refers to lesions that show histological evidence of invasion through the muscularias mucosa into the submucosa.[3] Besides, the 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 long-standing UC patients was 4.1% at 10 years, 14.1% at 20 years, 28% at 30 years, and 38.9% at 40 years, with CRC risk of 0.1%, 2.9%, 6.7%, 10.0%, respectively.[5] The hazard ratio of developing CRC in IBD patients with dysplasia compared to 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.

According to the SCENIC consensus, IBD-dysplasia is classified into visible and non-visible. And visible lesions are further divided into polypoid dysplasia (protruding from the mucosa into the lumen $\geqslant$ 2.5 mm) and non-polypoid dysplasia ($<$ 2.5 mm or no protrusion above the mucosa) dysplasia.[6] There is a strong association between HGD and synchronous[7] or metachronous[5] CRC, justifying colectomy as a reasonable treatment for patients with IBD-HGD. With regards 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 has medium risk (e.g., 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 well confirmed by meta-analysis with post-operation CRC risk of as low as 5/1000 person-years.[9] Data about cancer risk after resection of non-polypoid dysplasia in IBD are scarce. The submucosal fibrosis and obscure margin of non-polypoid dysplasia in IBD are responsible for technical difficulties in endoscopic resection.[11] With the development of endoscopic techniques, several studies started to fill the gap in the literature on endoscopic resection in the management of non-polypoid dysplasia.[12]

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

Objectives

This research protocol aims to report the methodology of a planned systematic review and meta-analysis that will evaluate the effectiveness (curative resection rate, etc.) and safety (recurrence, bleeding, perforation, etc.) of endoscopic treatment for the non-polypoid dysplasia in patients with inflammatory bowel disease.

METHODS AND ANALYSIS

The protocol was registered on the PROSPERO website (CRD42019120413) and reported in compliance with PRISMA-P statement.[13] Any further amendments in the protocol and conducting of this systematic review will be recorded and submitted to the

PROSPERO website and reported in the 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 randomized 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 inflammatory bowel disease and non-polypoid dysplasia 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 characterized 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 tumors (lesions reach a large (>10 mm) lateral diameter without increasing their height or protrusion above the mucosa).[6,14] Besides, as the term DALM is confusing and also used to describe all irregular, diffuse masses or plaque lesions in actively or previously inflamed areas of the colon, to avoid missing eligible studies, we will carefully check the definition of DALM and will only include those that fulfill the criteria of non-polypoid dysplasia.

Types of interventions

The 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 of non-polypoid dysplasia.[15] The secondary outcomes in this systematic review include en-bloc resection rate, complete 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.

Search methods for identification of studies

Potentially relevant studies will be searched using Medline, Embase, the Cochrane Controlled Register of Trials (CENTRAL), the Scopus, Web of Science, and clinicaltrials.gov registry from database inception up to 1 July 2019. Free text and MeSH terms relevant with endoscopy, inflammatory bowel disease, and dysplasia will be used in the literature search. No filter for study design will be used. Hand search of the bibliographies of relevant review and systematic review articles will be also conducted. There will be no language limitation in the literature search. Detailed literature search strategy is shown in Supplemental Table S1.

Data collection and analysis

Selection of studies

Records retrieved from literature search will be imported into Endnote and duplicated citations will be removed. Two investigators (CW and ZY) will independently assess the eligibility of the citations using the title and abstract and full texts of potentially eligible studies will be used to judge the final eligibility. Disagreement during the literature screening and inclusion will be resolved by discussion with a methodologist (ZYL). Reasons for excluding citations in each stage will be noted in Endnote library.

Data extraction and management

Data will be extracted into an Excel extraction form by one investigator (CW) and double-checked by one methodologist (ZYL). The following information will be extracted from each eligible study: 1) basic information of the study (author, publication

year, design); 2) patients' characteristics (age, sex, duration of disease, inflammatory endoscopic/histological activity, lesion size, lesion location, submucosal fibrosis and different types of IBD (UC and CD), primitive sclerosing cholangitis (PSC)); 3) detailed information of the endoscopic equipments for surveillance and techniques for therapy (WLE, CE, NBI, EMR, ESD, etc.); 4) outcome data (total number of patients receiving the endoscopic resection for non-polypoid dysplasia, number of patients with en-bloc/complete/curative resection (complete resection with submucosal invasion $<$ 1000 mm, absent lymphovascular involvement, good cell differentiation), postoperative bleeding and perforation, submucosal fibrosis, CRC incidence, local recurrence, and metachronous recurrence, and overall survival in long-term follow-up). We will make the largest use of all the available materials of the relevant studies, including but not limited to the publication for the main results and study design, unpublished report, information from study registry, and online appendices. If the key information was not reported in the above sources, we will try to contact the investigators to get the relevant data through email. All the extracted data will be transformed into the International System of Units.

Risk of bias assessment

If there were any evidence from randomised studies or two-armed cohort studies, we will use the Cochrane Collaboration's tool for assessing risk of bias in randomised controlled trials and the Newcastle-Ottawa Scale (NOS) to evaluate the risk of bias, respectively. 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 evaluated by one investigator (CW) and double checked by one methodologist (ZYL). Any disagreement will be resolved by discussion with a senior investigator (WD). Detailed criteria of the modified AHRQ tool are shown in Supplemental Table S2. Results from risk of bias assessment will be tabulated shown.

Statistical analysis

We will firstly describe the basic characteristics and risk of bias of eligible studies. If studies with different designs were eligible, they will be reported and synthesized separately. The eligible studies will be assessed in terms of heterogeneity by evaluating the clinical and methodological differences qualitatively, and if there was significant heterogeneity, quantitative synthesis will be abandoned.

This planned systematic review aims to collect evidence from randomized clinical trials and observational studies, however, we anticipate that the data of resection rate 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, random-effects model will be used 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 were enough data supporting for the synthesis.[18] Clopper-Pearson interval method will be used to estimate the CI in each individual study.[19]

The 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 considered as substantial heterogeneity.[21]

There is no planned assessment for reporting bias in this systematic review since the hypothesis behind the commonly applied methods for detecting reporting bias may not be satisfied in the meta-analysis for single-armed rate or proportions.[22]

Subgroup analysis will be conducted with regards to lesion size, lesion location, duration of the disease, submucosal fibrosis and different types of IBD (UC and CD). Post-hoc subgroup analysis will be conducted if there is evidence that some important 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 the statistical analysis will be completed in R (R Foundation for Statistical Computing, Vienna, Austria, version 3.5.2) with 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.

Role of funding source, ethics, conflict of interest, and dissemination

This systematic review and meta-analysis is funded by Peking Union Medical College (100232017). The sponsor has no role in study design, data collection, data analysis, and results interpretation. A formal ethical approval is waivered since there is no individual data involved in the analysis and all the combined results will be retrieved from study-level data. This is a research protocol for a systematic review and the data are not collected yet, hence, there is no data published in a data repository. The results will be disseminated through peer-reviewed publications or conference abstracts.

Competing Interest statement

All the authors declared that there was no conflict of interest.

Patient and Public Involvement

Patients and or public are not involved.

DISCUSSION

There exist technical difficulties for endoscopic resection of non-polypoid dysplasia due to indefinite margin and submucosal fibrosis. Our meta-analysis will evaluate the overall en-bloc/complete/curative resection rate and implement subgroup analysis according to potential influence factors such as lesion size, inflammatory activity to select patients who may benefit more from endoscopic therapy. In another aspect, taking into account the lack of evidence in natural history for non-polypoid dysplasia after endoscopic resection especially for metachronous dysplasia and CRC incidence rate,[6] this planned systematic review and meta-analysis will provide useful information of long-term prognosis. We will also compare our results with the evidence from polypoid dysplasia which was cited by ECCO[8] and SENIC[6] guidelines which may help to make reasonable therapeutic strategies for management of non-polypoid dysplasia in IBD. Besides, endoscopic resection has advantage for less complication risk and confirms to patients' preference,[24] therefore, if endoscopic resection is reasonable for management of non-polypoid dysplasia, it could be recommended as primary management. However, this systematic review may have some potential limitations. The best evidence evaluating the effect of endoscopic resection should come from randomized controlled trials comparing the endoscopic resection versus other therapies in patients with non-polypoid dysplasia in inflammatory bowel disease. However, based on our pilot literature search, few studies, if any, have addressed this problem in a randomized design. The data synthesis from a single-arm cohort studies or other relevant data sources may be highly sensitive to the selection of population and the practice setting, hence, there may be significant heterogeneity between studies. Moreover, the potential limited follow-up may be insufficient to observe enough cases for some long-term outcome events such as CRC incidence rate, local recurrence rate, and overall survival. The underlying heterogeneity regarding to clinical and methodological considerations should be evaluated using subgroup analysis or meta-regression. Nevertheless, the number of eligible studies are expected to be small given the relatively late application of this technique in practice, limiting our ability of

analyzing the impact factor of the treatment effectiveness.

CONTRIBUTION

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

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Supplementary Table 1. Literature search strategy in Medline.

#	Term
1	Exp Inflammatory bowel disease/
2	Crohn*.mp.
3	Ulcerative colitis*.mp
4	IBD.mp.
5	Inflammatory bowel disease*.mp.
6	OR/1-5
7	Exp Colonic Neoplasms/
8	(dysplas* OR neoplas* OR adenom* OR polyp*).mp.
9	DALM.mp.
10	colit* AND associat* AND (lesion* OR mass*).mp.
11	OR/7-10
12	6 AND 11
13	exp Endoscopic Mucosal Resection/
14	(endoscop* AND (therap* OR dissect* OR resect* OR treat*)).mp./ (endoscop* ADJ5 (therap* OR dissect* OR resect* OR treat*)).mp.
15	(ESD OR EMR OR EPMR OR ER).mp.
16	OR/13-15
17	12 AND 16

Supplementary Table 2. Detailed criteria to assess the risk of bias.

Domain	Item	Response
Selection bias	1.Did the study apply clear inclusion/exclusion criteria in the selection of participants?	Low risk, the study reported clear and appropriate inclusion/exclusion criteria; high risk, the criteria used in the study may lead to bias in the estimation of the curative resection rate; unclear, there is no relevant information.
	2.Were the participants representative of the targeted population?	Low risk, the participants were recruited consecutively or using probability sampling method; high risk, the participants in the study were biased from the targeted population; unclear, there is no relevant information.
Performance bias	1.Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?	Low risk, there was no concurrent or unintended intervention, or the existing concurrent intervention is unlikely to influence the resection rate; high risk, there were some concurrent or unintended intervention that may influence the resection rate; unclear, there is no relevant information.
	2.Did variation from the study protocol	Low risk, the reporting results are concordant with the information from registration and study protocol; high risk, there are some changes in the conducting of the study compared with the

Domain	Item	Response
	compromise the conclusions of the study?	registration or study protocol; unclear, there is no available registration or protocol.
Attrition bias	1.Was the follow-up completed in all subjects?	Low risk, the primary outcome (curative resection) could be assessed in more than or equal to 90% of the participants, or there is solid evidence indicating that those who lose to follow-up were similar with those still staying in the cohort; high risk, less than 90% of the participants contributed to the primary outcome; or there is evidence indicating that those who lose to follow-up were different with those still staying in the cohort; unclear, there is no relevant information.
Detection bias	1.Were the outcome assessors blinded to the intervention or exposure status of participants?	Low risk, the outcome assessor were totally blinded to the intervention; high risk, the outcome assessor knew the intervention; unclear, there is no relevant information.

Domain	Item	Response
	2.Were the inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?	Low risk, the personnel who recruited the participants were unaware of the intervention, or objective measures were used in the patients recruiting; high risk, the personnel who recruited the participants were aware of the intervention, or there is evidence that the recruiting of participants will lead to biased estimation of the primary outcome; unclear, there is no relevant information.
	3.Were primary outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Low risk, the personnel who assessed the outcome were unaware of the intervention, or objective measures were used in the primary outcome; high risk, the personnel who assessed the outcome were aware of the intervention, or there is evidence that the assessment of the primary outcome will lead to biased estimation; unclear, there is no relevant information.
Reporting bias	1.Were the potential outcomes pre-specified by	Low risk, all the predefined outcomes in registration or study protocol were reported in the study; high risk, the investigators selectively reported some predefined outcomes, or there are

Domain	Item	Response
	the researchers? Are all pre-specified outcomes reported?	changes in the outcomes of interest; unclear, there is no available registration or study protocol.

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	Page 2.
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a. This is not an update of a previous review.

	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2.
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page.
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 8.
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Page 2.
Sources	#5a	Indicate sources of financial or other support for the review	Page i and 7.
Sponsor	#5b	Provide name for the review funder and / or sponsor	Page i and 7.
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	Page 7.
Rationale	#6	Describe the rationale for the review in the context of what is already known	Page 1 to 2.
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 2.
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study	Page 2 to 3.

		design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 3.
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 4.
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 4.
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 4.
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 4.
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 4.

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 3.
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 5.
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	Page 6.
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	Page 6.
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 6 and 7.
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 6.
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 6 and 7.
Confidence in cumulative	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 7.

evidence

BMJ Open

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

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TITLE

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

AUTHORSHIP

Yue-Lun Zhang, PhD[1, 2]*, Wei Chen[1]*, Yi Zhao[1], Dong Wu, MD[1].

1 Department of Gastroenterology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College

2 Central Research Laboratory, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College

*These authors contributed equally and should be regarded as co-first authors.

Corresponding to Dr. Wu, Dong (wudong061002@aliyun.com, Department of Gastroenterology, Peking Union Medical College Hospital, 1 Shuaifuyuan, Dongcheng District, Beijing, China, 100730).

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ABSTRACT

Introduction

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

Methods and analysis

Medline, Embase, Cochrane Library, the Scopus, Web of Science, and clinical trials registry from database inception to the search date will be used to retrieve the 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 Ethcis Committee of Peking Union Medical College Hospital because there is 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.

Registration number

CRD42019120413.

Keywords

Non-polypoid dysplasia, inflammatory bowel diseases, endoscopy, systematic review, protocol.

Strengths and limitations of this study

- The planned quantitative synthesis addressing the endoscopic resection for non-polypoid in inflammatory bowel disease will overcome the limited statistical power in the previous original studies.
- There is no restriction on population, study design, or publication characteristics providing an overall evidence map for clinical practice.
- Limited evidences 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 characterized by specific cytological and/or architectural changes to the epithelium, and CRC refers to lesions that show histological evidence of invasion through the muscularias mucosa into the submucosa.[3] Besides, the 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 long-standing UC patients was 4.1% at 10 years, 14.1% at 20 years, 28.0% at 30 years, and 38.9% at 40 years, with CRC risk of 0.1%, 2.9%, 6.7%, 10.0%, respectively.[5] The hazard ratio of developing CRC in IBD patients with dysplasia compared to 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 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 $\geqslant$ 2.5 mm) and non-polypoid dysplasia ($<$ 2.5 mm or no protrusion above the mucosa) dysplasia.[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 regards 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 has medium risk (e.g., 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 post-operation CRC risk of as low as 5/1,000 person-years.[9] Data about CRC risk after resection of non-polypoid dysplasia in IBD are scarce. The submucosal fibrosis and obscure margin of non-polypoid dysplasia in IBD are responsible for 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 the non-polypoid dysplasia in patients with IBD.

METHODS AND ANALYSIS

The protocol was registered on the PROSPERO website (CRD42019120413) and reported in compliance with PRISMA-P statement.[13] Any further amendments in the protocol and conducting of this systematic review will be recorded and submitted to the PROSPERO website and reported in the 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 randomized 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 characterized 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 tumors (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 DALM and will only include those that fulfill the criteria of 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

The 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 ＜1,000 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, the Cochrane Controlled Register of Trials (CENTRAL), the Scopus, Web of Science, and clinicaltrials.gov registry from database inception up to 1 July 2019. Free text and MeSH 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 Supplemental Table S1.

Data collection and analysis

Selection of studies

Records retrieved from the literature search will be imported into Endnote, and duplicated citations will be removed. Two investigators (CW and ZY) will independently assess the eligibility of the studies by reading the title, abstract, and 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 (ZYL) and a gastroenterologist (WD). 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 (CW) and

double-checked by one methodologist (ZYL). We will retrieve the following information from each eligible study:

1) basic information of the study: author, publication year, design, sample size;

2) 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 (PSC);

3) detailed information of the endoscopic equipment for surveillance and techniques for therapy: WLE, CE, NBI, EMR, ESD, etc;

4) outcome data: number of patients with en-bloc/R0/curative resection, postoperative bleeding and perforation, submucosal fibrosis, CRC incidence, local recurrence, and 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 for assessing the risk of bias in randomised controlled trials and the Newcastle-Ottawa Scale (NOS) to evaluate the risk of bias in two-armed cohort studies, respectively. 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 evaluated by one investigator (CW) and double-checked by one methodologist (ZYL). Any disagreement will be resolved by discussion with a senior investigator (WD). Detailed criteria of the modified AHRQ tool are shown in Supplemental 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 synthesized 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, the quantitative synthesis will be abandoned.

This planned systematic review aims to collect evidences from randomized clinical trials and observational studies. However, we anticipate that the data of interested outcomes 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 for the synthesis.[18] Clopper-Pearson interval method will serve to estimate the 95% CI in each study.[19]

The 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 regards 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 the statistical analysis will be completed in R (R Foundation for Statistical Computing, Vienna, Austria, version 3.5.2) with 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 public are not involved in the design and conception of this study.

Ethics and dissemination

Formal ethical approval is waivered since there is no individual data involved in the analysis, and all the combined results will be retrieved from study-level data. This is a research protocol for a systematic review and the data are not collected yet, hence, there is 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 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

influence factors such as lesion size, inflammatory activity to select patients who may benefit most from endoscopic therapy. Given that the incidence of metachronous dysplasia and CRC remains largely unknow 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 SENIC[6] guidelines, which may help clinicians make reasonable therapeutic strategies for 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 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 the 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 analyze influencing factors for treatment effectiveness.

AUTHORS' CONTRIBUTIONS

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

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COMPETING INTERESTS

The authors declare that they have no conflict of interest.

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Supplementary Table 1. Literature search strategy in Medline.

#	Term
1	Exp Inflammatory bowel disease/
2	Crohn*.mp.
3	Ulcerative colitis*.mp
4	IBD.mp.
5	Inflammatory bowel disease*.mp.
6	OR/1-5
7	Exp Colonic Neoplasms/
8	(dysplas* OR neoplas* OR adenom* OR polyp*).mp.
9	DALM.mp.
10	colit* AND associat* AND (lesion* OR mass*).mp.
11	OR/7-10
12	6 AND 11
13	exp Endoscopic Mucosal Resection/
14	(endoscop* AND (therap* OR dissect* OR resect* OR treat*)).mp./ (endoscop* ADJ5 (therap* OR dissect* OR resect* OR treat*)).mp.
15	(ESD OR EMR OR EPMR OR ER).mp.
16	OR/13-15
17	12 AND 16

Supplementary Table 2. Detailed criteria to assess the risk of bias.

Domain	Item	Response
Selection bias	1.Did the study apply clear inclusion/exclusion criteria in the selection of participants?	Low risk, the study reported clear and appropriate inclusion/exclusion criteria; high risk, the criteria used in the study may lead to bias in the estimation of the curative resection rate; unclear, there is no relevant information.
	2.Were the participants representative of the targeted population?	Low risk, the participants were recruited consecutively or using probability sampling method; high risk, the participants in the study were biased from the targeted population; unclear, there is no relevant information.
Performance bias	1.Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?	Low risk, there was no concurrent or unintended intervention, or the existing concurrent intervention is unlikely to influence the resection rate; high risk, there were some concurrent or unintended intervention that may influence the resection rate; unclear, there is no relevant information.
	2.Did variation from the study protocol	Low risk, the reporting results are concordant with the information from registration and study protocol; high risk, there are some changes in the conducting of the study compared with the

Domain	Item	Response
	compromise the conclusions of the study?	registration or study protocol; unclear, there is no available registration or protocol.
Attrition bias	1.Was the follow-up completed in all subjects?	Low risk, the primary outcome (curative resection) could be assessed in more than or equal to 90% of the participants, or there is solid evidence indicating that those who lose to follow-up were similar with those still staying in the cohort; high risk, less than 90% of the participants contributed to the primary outcome; or there is evidence indicating that those who lose to follow-up were different with those still staying in the cohort; unclear, there is no relevant information.
Detection bias	1.Were the outcome assessors blinded to the intervention or exposure status of participants?	Low risk, the outcome assessor were totally blinded to the intervention; high risk, the outcome assessor knew the intervention; unclear, there is no relevant information.

Domain	Item	Response
	2.Were the inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?	Low risk, the personnel who recruited the participants were unaware of the intervention, or objective measures were used in the patients recruiting; high risk, the personnel who recruited the participants were aware of the intervention, or there is evidence that the recruiting of participants will lead to biased estimation of the primary outcome; unclear, there is no relevant information.
	3.Were primary outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Low risk, the personnel who assessed the outcome were unaware of the intervention, or objective measures were used in the primary outcome; high risk, the personnel who assessed the outcome were aware of the intervention, or there is evidence that the assessment of the primary outcome will lead to biased estimation; unclear, there is no relevant information.
Reporting bias	1.Were the potential outcomes pre-specified by	Low risk, all the predefined outcomes in registration or study protocol were reported in the study; high risk, the investigators selectively reported some predefined outcomes, or there are

Domain	Item	Response
	the researchers? Are all pre-specified outcomes reported?	changes in the outcomes of interest; unclear, there is no available registration or study protocol.

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	Page 2.
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a. This is not an update of a previous review.

	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2.
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page.
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 8.
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Page 2.
Sources	#5a	Indicate sources of financial or other support for the review	Page i and 7.
Sponsor	#5b	Provide name for the review funder and / or sponsor	Page i and 7.
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	Page 7.
Rationale	#6	Describe the rationale for the review in the context of what is already known	Page 1 to 2.
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 2.
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study	Page 2 to 3.

		design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 3.
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 4.
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 4.
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 4.
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 4.
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 4.

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 3.
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 5.
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	Page 6.
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	Page 6.
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 6 and 7.
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 6.
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 6 and 7.
Confidence in cumulative	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 7.

evidence