Efficacy of various endoscopic modalities in detecting dysplasia in ulcerative colitis: A systematic review and network meta-analysis

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Abstract

BACKGROUND
Longstanding ulcerative colitis (UC) is associated with an increased risk of colonic neoplasia. Various endoscopic modalities, such as chromoendoscopy (CE), narrow band imaging (NBI) and random biopsy have been introduced for surveillance, however, there exists a paucity of direct comparisons between them. We aimed to conduct a network meta-analysis of randomized controlled trials (RCTs) performed for surveillance of neoplasia in UC.

AIM
To provide a comparative evaluation of the efficacy of the above-mentioned various modalities.

METHODS
We searched MEDLINE/PubMed, Web of Science, Embase, Google Scholar and Cochrane Central Registry through May 2016 for RCTs evaluating the efficacy of endoscopic modalities for surveillance of neoplasia in UC. The primary outcomes of interest were dysplasia (low- or high-grade) detection rates per biopsy and per patient, and dysplasia numbers per patient. Studies were simultaneously analyzed using a random-effects network meta-analysis under the Bayesian framework to identify the modality with the highest dysplasia detection rate. The best ranking probability for the dysplasia detection rate was analyzed by surface under the cumulative ranking (SUCRA) technique.

RESULTS
Six prospective RCTs of a total 1038 patients were identified. We identified 4
INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) that causes inflammation of the colon and rectum. It may involve the rectum only, but many will experience progression and extension of disease to the proximal colon[1-3]. Due to the longstanding inflammation, patients with UC are at risk for colorectal cancer and dysplasia[4,5]. The risk is higher among those with pancolonic inflammation and with longer disease duration[5-7]. Current guidelines recommend endoscopic surveillance of CRC in patients with UC after 8-10 years of diagnosis[3,8-14].

Detection of dysplasia is often difficult as they can be subtle and difficult to discriminate between surrounding mucosa. For a long time, recommendations included random 4 quadrant non-targeted biopsies every 10 cm, resulting in a minimum of 32 biopsies per colonoscopy[15-18]. The random biopsy method is laborious and actually only a small area of the entire mucosal surface is biopsied. More recently, advanced modalities such as chromoendoscopy (CE) and narrow-band imaging (NBI) have been introduced to clinical practice[19]. They have shown improved detection of neoplasia in screening colonoscopies and have been applied to surveillance for dysplasia in UC[20-22]. Although retrospective and few prospective studies on dysplasia detection in UC have been performed, there exists a paucity of head-to-head comparisons between different modalities. Furthermore, the number of prospective randomized controlled trial (RCTs) is limited and the study population and treatment modality reported vary among studies.

Network meta-analysis is a type of meta-analysis in which multiple treatments are compared simultaneously. Different from pairwise analysis, network meta-analysis is capable of testing the relative effect of various endoscopic modalities and estimating the rank order of the best modality to use in UC surveillance.

Core tip: Ulcerative colitis (UC) is associated with increased neoplasia risk. Chromoendoscopy (CE), narrow band imaging (NBI) and random biopsy are used for surveillance, but data is limited to conclude best surveillance rank order. We did a network meta-analysis of UC surveillance randomized controlled trials. We identified 4 modalities; white light (WL) high definition (HD) or standard definition (SD), CE HD, and NBI HD. Results showed no differences among WL HD, NBI HD, and CE HD, while WL SD was inferior. The use of HD colonoscopes with or without image enhancement may provide improved detection of dysplasia in UC surveillance.
compared using direct comparisons of treatments, here in our case within RCTs, and indirect comparisons across RCTs based on a common comparator\[23,24\]. In order to provide a comparative evaluation among different endoscopic modalities and to rank the modalities based on their detection rate, we conducted a network meta-analysis comparing RCTs of surveillance for dysplasia in UC.

**MATERIALS AND METHODS**

**Data sources**
We searched MEDLINE (1993-July 2016), Google Scholar (1993-July 2016), Scopus (1993-July 2016), EMBASE (1993-July 2016), Web of Science (1980-July 2016) and Cochrane Central Register of Controlled Trials (through July 2016) for studies on UC dysplasia surveillance. For Google Scholar, only the first one thousand articles were reviewed as it does not provide results beyond it. We also searched abstracts from scientific meetings (American Gastroenterology Association, American College of Gastroenterology, United European Gastroenterology, 2001-2016), and bibliographies of identified articles for additional references.

**Search strategy and study selection**
To be eligible for inclusion, we only considered prospective RCTs evaluating the dysplasia detection in UC that compared outcomes between two or more different endoscopic modalities. We imposed no restrictions regarding age, sex, and duration of study but we tried to include studies with similar age, sex and duration ranges. We imposed no geographic or language restrictions and articles in languages other than English were translated if necessary. Two authors (Gondal B and Komaki Y) independently screened each of the potential titles and abstracts in the primary search to exclude studies that did not address the research question of interest. The full text of the remaining articles was examined to determine whether it contained relevant information and were eligible for inclusion. Areas of disagreement or uncertainty were resolved by consensus between the two authors. The corresponding authors of studies were contacted to provide additional information on trials if required. Studies were searched with a combination of terms including “UC”, “dysplasia”, “surveillance”, “cancer”, “chromoendoscopy”, “NBI”, “narrow band imaging” (both as medical subject headings and free text terms). These were combined by using the set operator and with studies identified with the terms.

**Data extraction and quality assessment**
All data were independently abstracted in duplicate by two authors (Gondal B and Komaki Y) by using a data abstraction form. Data on the study characteristics, such as author name, year of publication, study design, sample size, mean age of patients, type of scope and endoscopic modality used, total number of procedures, number of dysplastic lesions per random and targeted biopsy, and procedure withdrawal time, were collected. Studies that included patients with known neoplasia, colorectal cancer, poor preparation, severe inflammation, or no histology and fewer patients (less than 10) were excluded from the analysis. The Jadad score, a scale that assesses the methodological quality of a clinical trial, and Cochrane Risk of Bias Assessment Instrument were used to evaluate the methodological quality of the RCTs\[25,26\].

**Outcome assessment**
The primary outcome measures of interests were dysplasia detection rate per biopsy, dysplasia detection rate per patient, and numbers of dysplastic lesions detected per patients among different modalities. We also compared average procedure withdrawal times. Dysplastic lesions were defined as at least low-grade dysplasia per each study’s criteria. Results of the direct meta-analysis between modalities, where applicable, were also shown for reference in supplementary figures.

**Statistical analysis**
We followed the PRISMA for Network Meta-Analyses in the report of this meta-analysis\[27\]. The protocol of this meta-analysis has not been published or registered to any databases. A random-effects network meta-analysis using the Bayesian Markov chain Monte Carlo method was performed with ADDIS 1.16.1 and further details can be found at drugis.org\[28\]. Inconsistency and node-splitting models were applied to assess the consistency of the RCTs included in the network. Loop inconsistency models appeal directly to the intuition about how inconsistencies in networks of evidence might arise\[29\]. When loops of therapies were available, inconsistency factors were calculated to assess the strength of the data. The results were considered to show no significant inconsistency when 95% confidence intervals (95%CI) of inconsistency
factors included zero or when a large probability $P > 0.05$ for the comparison between direct and indirect effects in the node splitting analysis was shown. The ranking probability for each modality, i.e., the most efficacious, the second-best, the third-best, and so on, was calculated and the overall ranks were interpreted by surface under the cumulative ranking (SUCRA) technique. The larger SUCRAs denote better endoscopic modality. The effect sizes related to the studied outcomes and their corresponding 95%CI were also reported.

Direct meta-analysis was also performed with ADDIS 1.16.1 for reference. Odds ratio (OR) of detecting dysplasia were compared between the two groups. We evaluated the presence of heterogeneity across trials of each therapy by using the $I^2$ statistic. An $P < 25\%$ indicates low heterogeneity, 25%-75% moderate heterogeneity, and $> 75\%$ high heterogeneity, respectively. We followed the Cochrane Handbook for Systematic Reviews of Interventions in the report of this meta-analysis.

**RESULTS**

**Study characteristics**

We identified 2927 citations through literature search, excluded 2862 titles and abstracts after initial screening, and assessed 65 articles for eligibility (Figure 1). Upon detailed review, we further excluded 59 more articles, and ultimately included 6 prospective RCTs which looked at dysplasia detection rates in WL HD, WL SD, CE HD, and NBI HD. All the studies were parallel studies. A total of 1038 patients were included in the analysis for this network meta-analysis. The characteristics and outcomes of the included studies are summarized in Table 1. The quality of the studies assessed by the Jadad score showed a median of 3 (range 1-4). The majority of trials were rated to be of good methodological quality, despite most of the trials not mentioning the procedures for allocation, concealment and blinding of outcome assessment (Table 2).

**COMPARISON OF DYSPLASIA DETECTION RATES PER BIOPSY**

**Direct meta-analysis**

As shown in Supplementary Figure 1A, there were 4 studies that compared the effectiveness of WL HD vs NBI HD in detecting dysplasia per biopsy, and the pooled results showed superiority of NBI HD (OR: 5.71, 95%CI: 1.87-17.47). Significant heterogeneity was seen as shown by an $I^2$ value of 88.2%, which appeared due to variable outcomes between studies. A single study showed superiority of CE HD over WL SD and another study was in slight favor of NBI HD over CE HD (Supplementary Figure 1B and C). It was difficult to draw any conclusion from the direct meta-analyses as quantitative assessment of the effectiveness between the 4 modalities in detecting dysplasia per biopsy was not possible.

**Network meta-analysis**

The pictorial network of all modality comparisons analyzed for best modality in detecting dysplasia per biopsy is shown in Figure 2A. Figure 2B shows the OR of detecting dysplastic lesions per all biopsies analyzed by the network meta-analysis. CE HD and NBI HD were numerically superior to WL HD or WL SD modalities, but the differences were not statistically significant. Ranking probabilities for each modality in detecting dysplasia per biopsy are shown in Figure 2C. The rank probability of dysplasia detection interpreted by SUCRA was as follows (in ascending order of rank), NBI HD (0.78, 95%CI: 0.41-1.14), CE HD (0.66, 95%CI: 0.29-1.03), WL SD (0.33, 95%CI: -0.04-0.70) and WL HD (0.24, 95%CI: -0.13-0.61). The difference between NBI HD and CE HD was small, but their differences between the WL modalities were moderate suggesting that CE or NBI are more efficient in detecting dysplasia per biopsy than WL. Inconsistency model analysis and node-splitting analysis were not possible as no loop was created among the modalities (Figure 2A).

**COMPARISON OF DYSPLASIA DETECTION RATES PER PATIENT**

**Direct meta-analysis**

Direct meta-analysis of 4 studies showed no difference between NBI HD vs WL HD
Table 1 The characteristics and outcomes of the included studies

| Study                  | Ref.          | Design   | Reference | Comparator | Disease Type, Age | Patients with dysplasia/totalpatients (n) | Bx with dysplasia/total bx (n) | Patients with dysplasia/total patients (n) | Bx with dysplasia/total Bx (n) | Patients with dysplasia/total patients (n) |
|------------------------|---------------|----------|-----------|------------|-------------------|------------------------------------------|----------------------------------|------------------------------------------|----------------------------------|------------------------------------------|
| NBI HD vs WL HD        | Dekker et al[32], 2007 | PRCT     | NBI HD    | WL HD      | UC, Adults        | 9/52                                      | 8/42                            | 9/42                                      | 21/1550                          | 7/42                                      |
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0.99), CE HD (0.48, 95%CI: 0.11-0.84) and WL SD (0.03, 95%CI: -0.33-0.40). The differences between the first three modalities were moderate, and the differences between WL SD and the rest were large without overlap of 95%CIs. It was suggested that WL SD appeared to be inferior to the other modalities.

Inconsistency model analysis and node-splitting analysis were not possible as no loop was created among the modalities (Figure 4A).

**DISCUSSION**

Our comprehensive network meta-analysis simultaneously compared various endoscopic modalities for dysplasia surveillance in UC. A few direct meta-analyses comparing two modalities have been previously reported, however, the rationale of our study was to add evidence through indirect comparisons by network meta-analysis, where direct head-to-head comparisons were lacking. On a per biopsy basis, NBI HD or CE HD appeared to be more effective compared to WL modalities. For detecting dysplasia on a per patient basis, though, WL HD and NBI HD, ranked relatively close, and over other modalities. Another finding is that WL SD consistently ranked worse compared to the other three modalities suggesting that its use cannot be rationalized for dysplasia surveillance in UC. Overall, the results of our study suggest that the use of a HD colonoscope may be more important rather than the use of image enhancing in detecting dysplasia in patients with UC.

The rank order of efficacy in the present network meta-analysis is somewhat different from various international societal recommendations where CE is recommended over other modalities. CE has been increasingly used in surveillance of dysplasia in UC since Kiesslich et al[36] reported its effectiveness over the traditional random biopsy method. Since then, many cohort studies have demonstrated the utility of CE which has led to its inclusion and recommendation in guidelines. However, the number of RCT showing the effectiveness of CE over random biopsy is small and the evidence supporting its use may not be robust. NBI system is one of the most commonly used image enhanced technology which has been shown to be effective in detecting colonic neoplasia in colon cancer screening. NBI with target biopsy has not been shown to be consistently more effective than WL exam, however, a recent study by Watanabe et al[37] showed its non-inferiority over CE. It was thus difficult to draw any conclusion from the existing RCT whether WL, CE or NBI were superior to or similar to each other by means of dysplasia detection in UC surveillance. Furthermore, some modalities lacked direct comparisons by RCT.
Table 2  Jadad score and Cochrane Risk of Bias Assessment Instrument

| Ref. | Was the study described as randomized? | Was the randomization scheme described and appropriate? | Was the study described as double-blind? | Was the method of double blinding appropriate? | Was there a description of dropouts and withdrawals? | Total Jadad score | Sequence generation (for arm randomization) | Allocation concealed | Blinding of outcomes | Incomplete outcome data addressed | ITT | Sample size calculation |
|------|-------------------------------------|--------------------------------------------------------|----------------------------------------|-------------------------------------------|-----------------------------------------------|-----------------|-------------------------------------------|-------------------|-----------------|-------------------------------|-----|------------------------|
| Dekker et al.[32], 2006              | o                                   | o                                           | o                                      | o                                          | x                                            | 4               | x                                          | x                 | o               | o                             | o   | o                      |
| Van den Broek et al.[33], 2011       | o                                   | NA                                         | x                                      | NA                                        | 1                                            | ?               | ?                                          | ?                 | x               | o                             | o   | x                      |
| Ignjatovic et al.[34], 2012          | o                                   | NA                                         | NA                                     | o                                         | 3                                            | ?               | ?                                          | ?                 | ?               | o                             | o   | o                      |
| Leifeld et al.[35], 2015             | o                                   | NA                                         | x                                      | NA                                        | 1                                            | o               | o                                          | x                 | ?               | ?                             | x   | ?                      |
| Kiesslich et al.[36], 2003           | o                                   | o                                          | o                                      | NA                                        | 4                                            | o               | o                                          | o                 | o               | o                             | o   | o                      |
| Watanabe et al.[37], 2016            | o                                   | o                                          | o                                      | NA                                        | 4                                            | o               | o                                          | o                 | o               | o                             | o   | o                      |

ITT: Intention to treat; NA: Not available.

The fundamental rationales of our network meta-analysis were to overcome the lack of direct comparisons of modalities and to perform indirect comparisons to objectively assess their comparative efficacy in detecting dysplasia. Network meta-analysis is now widely recognized and utilized in clinical questions where direct comparisons among treatments are not possible[38,39]. It can simultaneously compare multiple treatments by using direct comparisons of treatments within RCTs and indirect comparisons across RCTs based on a common comparator[23]. This analytical approach is justified when its key assumptions are satisfied, and we acknowledged the methodological challenge while calculating and interpreting statistics carefully.

We analyzed four different endoscopic modalities assessed in 7 head to head RCTs; WL SD, WL HD, CE HD (methylene blue or indigo carmine) and NBI HD. We found that among the 4 endoscopic modalities, NBI HD was the best modality for dysplasia detection per biopsy, but WL HD ranked slightly higher in terms of dysplasia per patient or numbers of dysplasia per patient. We acknowledge that our result was not solid enough to conclude that any one modality was the best and further investigation including larger RCTs is warranted. However, it does appear that WL SD appears to be inferior to the other modalities and its use cannot be justified based on the results of our network meta-analysis. Until further evidence is available, the use of NBI HD, WL HD and CE HD can all be utilized for dysplasia surveillance in UC. This is supported by observational studies demonstrating low yield of random biopsies compared to target biopsies[40].

One of the shortcomings of this network meta-analysis is that the number of included studies was relatively small with only one study comparing outcomes between CE HD vs NBI HD or CE HD vs WL SD. There were no studies comparing CE HD to WL HD or WL SD to WL HD, which resulted in a lack of loop of comparisons. Thus, we were unable to perform any inconsistency model analysis and node-splitting analysis in the subgroup analysis due to the lack of a loop among the comparison of included studies. Some studies included in our meta-analysis had potential risks of bias related to allocation concealment and blinding of outcome assessment, however, the median Jadad score was 3 and the majority of trials were rated to be of good methodological quality.

In conclusion, this systematic review and network meta-analysis comparing multiple modalities used in UC dysplasia surveillance suggests that the three
Figure 2  Network meta-analysis of different endoscopic modalities for dysplasia detection rates per biopsy.

A: Network of modality comparisons. Numbers indicate the number of studies comparing the two connected modality arms.

B: Relative effects of detecting dysplastic lesions. The numbers in the cell represent the odds ratio (95%CI) of the column defining modality relative to the row defining modality.

C: Rank probabilities (Consistency model) (No.1 is the best).

Figure 2  Network meta-analysis of different endoscopic modalities for dysplasia detection rates per biopsy. A: Network of modality comparisons. Numbers indicate the number of studies comparing the two connected treatment arms; B: Relative effects of detecting dysplastic lesions. The numbers in the cell represent the odds ratio (95% Confidence Intervals) of the column defining modality relative to the row defining modality; C: Rank probabilities (Consistency model) for each modality based on dysplasia outcome. Indicated is the possibility of each rank and the overall rank interpreted by surface under the cumulative ranking technique. NBI: Narrow band imaging; CE: Chromoendoscopy; WL: White light; HD: High definition; SD: Standard definition.

Modalities, WL HD, NBI HD and CE HD, showed overall similar effectiveness in detecting dysplasia. WL SD consistently ranked worse compared to the other modalities suggesting the importance of using a HD colonoscope.
Figure 3  Network meta-analysis of different endoscopic modalities for dysplasia detection rates per patient. A: Network of modality comparisons. Numbers indicate the number of studies comparing the two connected modality arms. B: Relative effects of detecting dysplastic lesions (The numbers in the cell represent the odds ratio (95%CI) of the column defining modality relative to the row defining modality). C: Rank probabilities (Consistency model) (No.1 is the best).
ARTICLE HIGHLIGHTS

Research background
Patients with ulcerative colitis (UC), which is a chronic inflammation of the colon and rectum, are at high risk of developing colorectal cancer (CRC), mainly if the inflammation involves the whole colon and/or lasts for a long duration. Currently, it is recommended to perform endoscopic surveillance looking for colon cancer and dysplasia in those patients after 8-10 years from the diagnosis of UC. Our study compares the best modality to use for early detection of dysplasia.

Research motivation
The main modalities used in CRC surveillance in UC are white light high definition (WL HD), WL standard definition (WL SD), chromoendoscopy (CE) HD, and narrow-band imaging (NBI) HD. There is a paucity of head-to-head comparison among these modalities to help physician in deciding what is the best option to use for early detection of dysplasia. This study is constructed to assist the clinician to choose the best yielding modality.

Research objectives
The main objective is to demonstrate the best modality to use in terms of detecting dysplasia and targeted biopsies. We realized that not all the modalities are equal in efficacy nor in yielding results. These objectives would be of major impact in future research and clinical practice.

Research methods
The research methods (e.g., experiments, data analysis, surveys, and clinical trials) that were adopted to realize the objectives, as well as the characteristics and novelty of these research methods, should be described in detail. The methods used to reach these objectives were literature search of studies on UC dysplasia surveillance on MEDLINE, Google Scholars, Scopus, Embase, Web of Science, and Cochrane Central Register of Controlled Trials (CRC). Only prospective randomized controlled trials (RCTs) evaluating the dysplasia detection in UC that compared outcomes between two or more different endoscopic modalities were included. Data
were extracted independently using a data abstraction form. Jadad score, a scale that assesses the methodological quality of a clinical trial, and Cochrane Risk of Bias Assessment Instrument were used to evaluate the methodological quality of the RCTs.

**Research results**

We found that for dysplasia per biopsy basis, the best modalities were NBI HD and CE HD, while on dysplasia per patient basis, WL HD and NBI HD were the highest ranked. For dysplasia numbers per patient, the three HD modalities were superior to WL SD. The striking finding was that regardless of the image enhancing modality used, HD was the most important option in detecting dysplasia. These finding could help the clinician in choosing the best yielding modality to use for CRC/dysplasia surveillance in patients with UC.

**Research conclusions**

Regardless of the image enhancing modality used, HD was the most important option in detecting dysplasia in patients with UC. When HD colonoscopes are used, image enhancing modality may not be required in detecting dysplasia in patients with UC. HD was the most important option in detecting dysplasia in patients with UC. The best modality to use in surveillance colonoscopies of UC was unclear. Based on the current guidelines for colorectal cancer surveillance in patients with ulcerative colitis, we found that HD is the best option in detecting dysplasia, while white light standard definition is the most inferior option. The increased use of HD would yield the best results in both dysplasia detection rate and targeted biopsies.

**Research perspectives**

Not all imaging or endoscopic modalities are equal in detecting dysplasia in UC. More data and research required to decide what is the single best modality to use for CRC/dysplasia surveillance in patients with UC. RCTs simultaneously comparing multiple modalities or a follow-up network meta-analysis when more studies become available.

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**REFERENCES**

1. Ekbom A, Helmqvist CG, Zack M, Holmberg L, Adami HO. Survival and causes of death in patients with inflammatory bowel disease: a population-based study. Gastroenterology 1992; 103: 954-960 [PMID: 1499945 DOI: 10.1016/0016-5085(92)90029-X]
2. Chol PM, Zelig MP. Similarity of colorectal cancer in Crohn's disease and ulcerative colitis: implications for carcinogenesis and prevention. Gut 1994; 35: 950-954 [PMID: 8063223 DOI: 10.1136/gut.35.7.950]
3. Farrar F, Odze RD, Eaden J, Itzkowitz SH. AGA technical review on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. Gastroenterology 2010; 138: 746-774, 774.e1-4; quiz e12-13 [PMID: 20141809 DOI: 10.1053/j.gastro.2009.12.035]
4. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 2001; 48: 526-535 [PMID: 11247898 DOI: 10.1136/gut.48.4.526]
5. Ekbom A, Helmqvist C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer. A population-based study. N Engl J Med 1990; 323: 1228-1233 [PMID: 2215606 DOI: 10.1056/NEJM1990101331802]
6. Itzkowitz SH, Harpaz N. Diagnosis and management of dysplasia in patients with inflammatory bowel diseases. Gastroenterology 2004; 126: 1634-1648 [PMID: 15168373 DOI: 10.1053/j.gastro.2004.03.025]
7. Langhol E, Munkholm P, Davidsen M, Binder V. Colorectal cancer risk and mortality in patients with ulcerative colitis. Gastroenterology 1992; 103: 1444-1451 [PMID: 1358741 DOI: 10.1016/0016-5085(92)91163-X]
8. Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults. American College Of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol 2010; 105: 501-23; quiz 524 [PMID: 2068562] DOI: 10.1038/ajg.2009.227]
9. Ullman T, Odze R, Farrar FA. Diagnosis and management of dysplasia in patients with ulcerative colitis and Crohn's disease of the colon. Inflamm Bowel Dis 2009; 15: 630-638 [PMID: 18942763 DOI: 10.1002/ibd.20766]
10. Jacucci M, Uraoka T, Fort Gasia M, Yahagi N. Novel diagnostic and therapeutic techniques for surveillance of dysplasia in patients with inflammatory bowel disease. Can J Gastroenterol Hepatol 2014; 28: 361-370 [PMID: 25157526 DOI: 10.1155/2014/825947]
11. Itzkowitz SH, Present DH; Crohn's and Colitis Foundation of America Colon Cancer in IBD Study Group. Consensus conference: Colorectal cancer screening and surveillance in inflammatory bowel disease. Inflamm Bowel Dis 2005; 11: 314-321 [PMID: 15735438 DOI: 10.1097/01.mib.0000160811.76729.d5]
12. Eaden JA, Mayberry JF; British Society for Gastroenterology; Association of Coloproctology for Great Britain and Ireland. Guidelines for screening and surveillance of asymptomatic colorectal cancer in patients with inflammatory bowel disease. Gut 2002; 51 Suppl 5: V10-V12 [PMID: 12221032 DOI: 10.1136/gut.51.Suppl.5.V10]
13. Cairns SR, Scholefield JH, Steele RJ, Dunlop MG, Thomas HJ, Evans GD, Eaden JA, Rutter MD, Atkin WP, Saunders BP, Lucassen A, Jenkins P, Fairclough PD, Woodhouse CR; British Society of Gastroenterology; Association of Coloproctology for Great Britain and Ireland. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut 2010; 59.
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666-689 [PMID: 20427401 DOI: 10.1136/gut.2009.179804]

Huguet JM, Suárez P, Ferrer-Barceló L, Ruiz L, Monzó A, Durá AB, Sempere J. Endoscopic recommendations for colorectal cancer screening and surveillance in patients with inflammatory bowel disease: Review of general recommendations. World J Gastrointest Endosc 2017; 9: 255-262 [PMID: 28690768 DOI: 10.4253/wjge.v9i6.255]

Jess T, Loftus EV, Velayos FS, Harmsen WS, Zinsmeister AR, Smyrk TC, Schlech CD, Tremaine WJ, Melton LJ, Mukhopadhy P, Sandborn WJ. Risk of intestinal cancer in inflammatory bowel disease: a population-based study from Olmsted County, Minnesota. Gastroenterology 2006; 130: 1039-1046 [PMID: 16618397 DOI: 10.1053/j.gastro.2005.12.037]

Loftus EV. Epidemiology and risk factors for colorectal dysplasia and cancer in ulcerative colitis. Gastroenterol Clin North Am 2006; 35: 517-531 [PMID: 16952738 DOI: 10.1016/j.gct.2006.07.005]

East JE, Toyomaga T, Suzuki N. Endoscopic management of nonpolyloid colorectal lesions in colonic IBD. Gastrointest Endosc Clin N Am 2014; 24: 435-445 [PMID: 24975534 DOI: 10.1016/j.gi.2014.03.003]

Leighton JA, Shen B, Baron TH, Adler DG, Davila R, Egan JV, Faigel DO, Gan SI, Hirota WK, Lichtenstein D, Qureshi WA, Rajan E, Zuckerman MJ, VanGuilder T, Fennell RD; Standards of Practice Committee, American Society for Gastrointestinal Endoscopy. ASGE guideline: endoscopy in the diagnosis and treatment of inflammatory bowel disease. Gastroenterol Endosc 2006; 63: 558-565 [PMID: 16564852 DOI: 10.1016/j.gastoint.2006.02.005]

Laine L, Kaltenbach T, Burkam A, McQuaid KR, Subramanian V, Söötkin R; SCENIC Guideline Development Panel. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. Gastroenterology 2015; 148: 639-651.e28 [PMID: 25720852 DOI: 10.1053/j.gastro.2015.01.031]

Annesse V, Daperno M, Rutter MD, Amiot A, Bossuyt P, East J, Ferrante M, Götz M, Katsanos KH, Kielbich R, Ordas I, Recipi A, Rosa B, Sebastian S, Kucharzik T, Eliaikm R; European Crohn's and Colitis Organisation. European evidence based consensus for endoscopy in inflammatory bowel disease. J Crohns Colitis 2013; 7: 982-1018 [PMID: 2418471 DOI: 10.1016/j.crohns.2013.09.011]

Gono K, Ohi T, Yamaguchi M, Ohyama N, Machida H, Sano Y, Yoshida S, Hamamoto Y, Endo T. Appearance of enhanced tissue features in narrow-band endoscopic imaging. J Biomed Opt 2004; 9: 568-577 [PMID: 15189905 DOI: 10.1117/1.1695663]

Rutter MD, Saunders BP, Schofield G, Forbes A, Price AB, Talbot IC. Pancolonic indigo carmine dye spraying for the detection of dysplasia in ulcerative colitis. Gut 2004; 53: 256-260 [PMID: 14742160 DOI: 10.1136/gut.2003.016396]

Mills EJ, Thorlund K, Ioannidis JP. Demystifying trial networks and network meta-analysis. BMJ 2013; 346: e2914 [PMID: 23674332 DOI: 10.1136/bmj.e2914]

Kokki H, Komaki F, Micic D, Yamada A, Suzuki Y, Sakuraba A. Pharmacologic therapies for severe steroid refractory hospitalized ulcerative colitis: A network meta-analysis. J Gastroenterol Hepatol 2017; 32: 1143-1151 [PMID: 27957761 DOI: 10.1111/j.gjhep.13674]

Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. England: Wiley 2008; 672

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996; 17: 1-12 [PMID: 8721797 DOI: 10.1016/0197-2456(95)00134-4]

Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Strauss S, Thorlund K, Jansen JP, Mulrow C, Catalá-López F, Gøtzsche PC, Dickersin K, Bontour I, Altman DG, Moher D. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015; 162: 777-784 [PMID: 26030634 DOI: 10.7322/M14-2385]

Gertvan Valkenhoef T, TijzZwinkels, Bertde Brock, HansHillege. ADDIS: A decision support system for evidence-based medicine. Decision Support Systems 2013; 55: 459-475 [DOI: 10.1016/j.dss.2012.10.005]

Jackson D, Doddington P, White IR. The design-by-treatment interaction model: a unifying framework for modelling loop inconsistency in network meta-analysis. Res Synth Methods 2016; 7: 329-332 [PMID: 26588593 DOI: 10.1002/jrsm.1188]

Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011; 64: 163-171 [PMID: 20688472 DOI: 10.1016/j.jclinepi.2010.03.016]

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-560 [PMID: 12981820 DOI: 10.1136/bmj.327.7414.557]

Dekker E, van den Broek FJ, Reitsma JB, Hardwicke JC, Offerhaus GJ, van Deventer SJ, Hommes DW, Fockens P. Narrow-band imaging compared with conventional colonoscopy for the detection of dysplasia in patients with longstanding ulcerative colitis. Endoscopy 2007; 39: 216-221 [PMID: 17385108 DOI: 10.1055/s-2007-966214]

van den Broek FJ, Fockens P, van Eeden S, Stokkers PC, Ponsioen CY, Reitsma JB, Dekker E. Narrow-band imaging versus high-definition endoscopy for the diagnosis of neoplasia in ulcerative colitis. Endoscopy 2011; 43: 108-115 [PMID: 21658822 DOI: 10.1055/s-0030-1259596]

Ignotovich A, East JE, Subramanian V, Suzuki N, Guenther T, Palmer N, Bassett P, Ragunath K, Saunders BP. Narrow band imaging for detection of dysplasia in colitis: a randomized controlled trial. Am J Gastroenterol 2012; 107: 885-890 [PMID: 22613903 DOI: 10.1038/aig.2012.67]

Leifeld L, Rogler G, Stallmach A, Schmidt C, Zuber-Jerger I, Hartmann F, Plauth M, Drabik A, Hofstätter F, Dieses HP, Kruis W; Detect Dysplasia Study Group. White-Light or Narrow-Band Imaging Colonoscopy in Surveillance of Ulcerative Colitis: A Prospective Multicenter Study. Clin Gastroenterol Hepatol 2015; 13: 1776-1781.e1 [PMID: 25952309 DOI: 10.1016/j.cgh.2015.04.172]

Kieslich R, Fritsch J, Holtmann M, Koehler HH, Stolte M, Kanzler S, Nafe B, Jung M, Galle PR, Neurath MF. Methylene blue-aided chromoendoscopy for the detection of intraphlebitic neoplasia and colon cancer in ulcerative colitis. Gastroenterology 2003; 124: 880-888 [PMID: 12671882 DOI: 10.1053/gast.2003.50146]

Watanabe N, Yoshimatsu F, Kurosaki T, Matsumoto S, Oka S, Nishiya S, Fujii S. 722 Comparison Between Newly-Developed Narrow Band Imaging and Panchromatic Imaging for Surveillance Colonoscopy in Patients With Longstanding Ulcerative Colitis: A Prospective Multicenter Randomized Controlled Trial, Navigator Study. Gastrointestinal Endoscopy 2016; 83: AB172 [DOI: 10.1016/j.gie.2016.03.147]
38 Bonovas S, Fiorino G, Allocca M, Lytras T, Nikolopoulos GK, Peyrin-Biroulet L, Danese S. Biologic Therapies and Risk of Infection and Malignancy in Patients With Inflammatory Bowel Disease: A Systematic Review and Network Meta-analysis. *Clin Gastroenterol Hepatol* 2016; 14: 1385-1397.e10 [PMID: 27189910 DOI: 10.1016/j.cgh.2016.04.039]

39 Vickers AD, Ainsworth C, Mody R, Bergman A, Ling CS, Medjedovic J, Smyth M. Systematic Review with Network Meta-Analysis: Comparative Efficacy of Biologics in the Treatment of Moderately to Severely Active Ulcerative Colitis. *PLoS One* 2016; 11: e0165435 [PMID: 27776175 DOI: 10.1371/journal.pone.0165435]

40 Dohil R, Newbury R, Fox L, Bastian J, Aceves S. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. *Gastroenterology* 2010; 139: 418-429 [PMID: 20457157 DOI: 10.1053/j.gastro.2010.05.001]
