

World Journal of *Gastroenterology*

World J Gastroenterol 2018 September 21; 24(35): 3965-4092



**EDITORIAL**

- 3965 Role of endoscopic therapy in early esophageal cancer
Malik S, Sharma G, Sanaka MR, Thota PN
- 3974 Biomarkers for hepatocellular carcinoma: What's new on the horizon?
Ocker M

REVIEW

- 3980 Pediatric hepatocellular carcinoma
Khanna R, Verma SK
- 4000 Changing role of histopathology in the diagnosis and management of hepatocellular carcinoma
Rastogi A

MINIREVIEWS

- 4014 Endoscopy in inflammatory bowel disease: Role in diagnosis, management, and treatment
Spiceland CM, Lodhia N
- 4021 Biosimilars in paediatric inflammatory bowel disease
Sieczkowska-Golub J, Jarzebicka D, Oracz G, Kierkus J

ORIGINAL ARTICLE**Basic Study**

- 4028 Adiponectin affects the mechanical responses in strips from the mouse gastric fundus
Idrizaj E, Garella R, Castellini G, Mohr H, Pellegata NS, Francini F, Ricca V, Squecco R, Baccari MC
- 4036 Daikenchuto (Da-Jian-Zhong-Tang) ameliorates intestinal fibrosis by activating myofibroblast transient receptor potential ankyrin 1 channel
Hiraishi K, Kurahara LH, Sumiyoshi M, Hu YP, Koga K, Onitsuka M, Kojima D, Yue L, Takedatsu H, Jian YW, Inoue R

Retrospective Cohort Study

- 4054 Portosplenomesenteric vein thrombosis in patients with early-stage severe acute pancreatitis
Ding L, Deng F, Yu C, He WH, Xia L, Zhou M, Huang X, Lei YP, Zhou XJ, Zhu Y, Lu NH

Retrospective Study

- 4061 Serum anti-*Helicobacter pylori* antibody titer and its association with gastric nodularity, atrophy, and age: A cross-sectional study
Toyoshima O, Nishizawa T, Sakitani K, Yamakawa T, Takahashi Y, Yamamichi N, Hata K, Seto Y, Koike K, Watanabe H, Suzuki H

**Observational Study**

- 4069** Real-life chromoendoscopy for dysplasia surveillance in ulcerative colitis

Klepp P, Tollisen A, Røseth A, Cvancarova Småstuen M, Andersen SN, Vatn M, Moum BA, Brackmann S

Randomized Clinical Trials

- 4077** Usefulness of the clip-flap method of endoscopic submucosal dissection: A randomized controlled trial

Ban H, Sugimoto M, Otsuka T, Murata M, Nakata T, Hasegawa H, Inatomi O, Bamba S, Andoh A

CASE REPORT

- 4086** Infant cholestasis patient with a novel missense mutation in the *AKR1D1* gene successfully treated by early adequate supplementation with chenodeoxycholic acid: A case report and review of the literature

Wang HH, Wen FQ, Dai DL, Wang JS, Zhao J, Setchell KDR, Shi LN, Zhou SM, Liu SX, Yang QH

ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Amedeo Lonardo, MD, Doctor, Senior Lecturer, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena 41126, Italy

AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 642 experts in gastroenterology and hepatology from 59 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

INDEXING/ABSTRACTING

World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2018 edition of Journal Citation Reports® cites the 2017 impact factor for *WJG* as 3.300 (5-year impact factor: 3.387), ranking *WJG* as 35th among 80 journals in gastroenterology and hepatology (quartile in category Q2).

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: Xiang Li
Responsible Electronic Editor: Shu-Yu Yin
Proofing Editor-in-Chief: Lian-Sheng Ma

Responsible Science Editor: Xue-Jiao Wang
Proofing Editorial Office Director: Ze-Mao Gong

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski, MD, PhD, DSc (Med),
Professor of Medicine, Chief Gastroenterology, VA
Long Beach Health Care System, University of California, Irvine, CA, 5901 E. Seventh Str., Long Beach, CA 90822, United States

EDITORIAL BOARD MEMBERS

All editorial board members resources online at <http://www.wjgnet.com/1007-9327/editorialboard.htm>

EDITORIAL OFFICE

Ze-Mao Gong, Director
World Journal of Gastroenterology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

PUBLISHER

Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

PUBLICATION DATE

August 28, 2018

COPYRIGHT

© 2018 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

Full instructions are available online at <http://www.wjgnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION

<http://www.f6publishing.com>

Observational Study

Real-life chromoendoscopy for dysplasia surveillance in ulcerative colitis

Pasquale Klepp, Anita Tollisen, Arne Røseth, Milada Cvancarova Småstuen, Solveig N Andersen, Morten Vatn, Bjørn A Moum, Stephan Brackmann

Pasquale Klepp, Anita Tollisen, Arne Røseth, Unger-Vetlesen Institute, Department of Internal Medicine, Lovisenberg Diaconal Hospital, Oslo 0456, Norway

Pasquale Klepp, Milada Cvancarova Småstuen, Morten Vatn, Bjørn A Moum, Stephan Brackmann, Institute of Clinical Medicine, University of Oslo, Oslo 0317, Norway

Solveig N Andersen, Department of Pathology, Akershus University Hospital, Lørenskog 1474, Norway

Bjørn A Moum, Department of Gastroenterology, Oslo University Hospital, Oslo 0450, Norway

Stephan Brackmann, Department of Gastroenterology, Akershus University Hospital, Lørenskog 1474, Norway

ORCID number: Pasquale Klepp (0000-0002-0477-691X); Anita Tollisen (0000-0002-4776-9808); Arne Røseth (0000-0003-0916-5111); Milada Cvancarova Småstuen (0000-0001-8947-8649); Solveig N Andersen (0000-0002-4814-8894); Morten Vatn (0000-0002-1179-4550); Bjørn A Moum (0000-0002-5884-4543); Stephan Brackmann (0000-0001-6434-0571).

Author contributions: Klepp P contributed to acquisition, analysis and interpretation of the data, and drafting and revision of the manuscript; Tollisen A contributed to planning and collection of the data; Røseth A contributed to conception and design of the study, and performed critical revision of the manuscript for important intellectual content; Cvancarova Småstuen M contributed to the statistical analysis and critical revision of the manuscript for important intellectual content; Andersen SN provided technical support and contributed to revision of the histopathological material; Vatn M provided critical revision of the manuscript for important intellectual content and performed study supervision; Moum BA and Brackmann S contributed to conception and design of the study, and performed critical revision of the manuscript for important intellectual content and study supervision; all authors have approved the final draft.

Supported by the Unger-Vetlesen Institute, Department of Internal Medicine, Lovisenberg Hospital.

Institutional review board statement: The study protocol was designed according to the combined knowledge and expertise of Assistant Professor Stephan Brackmann (Akershus University Hospital), Professor Bjørn A Moum (Oslo University Hospital) and Professor Morten Vatn (University of Oslo). The study protocol was approved by the Regional Committee for Medical and Health Research Ethics (REC Project NO. 2010/1093).

Informed consent statement: Written informed consent was collected from subjects prior to study inclusion.

Conflict-of-interest statement: The authors have no conflicts of interest.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement, and the manuscript was prepared and revised according to the STROBE Statement.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Pasquale Klepp, MD, Attending Doctor, Department of Internal Medicine, Lovisenberg Hospital, Lovisenberggt.17, Oslo 0456, Norway. pasklepp@gmail.com
Telephone: +47-23225000

Received: May 30, 2018

Peer-review started: May 30, 2018

First decision: July 4, 2018

Revised: August 6, 2018

Accepted: August 24, 2018

Abstract

AIM

To evaluate the use of chromoendoscopy for surveillance of ulcerative colitis in a real-life community hospital setting.

METHODS

Patients with extensive ulcerative colitis, having disease duration of more than 8 years and who presented between the years of 1999 to 2013, were offered enrolment in this single cohort prospective study. All participants underwent standard bowel preparation with sodium phosphate and chromoendoscopy. Two expert endoscopists, novice to chromoendoscopy, evaluated each segment of the colon with standard-definition colonoscopes after spray application of 0.4% indigo carmine. All observed lesions were recorded and evaluated before being removed and/or biopsied. In addition, nontargeted biopsies were taken from each segment of the colon. The dysplasia detection rate and dysplasia detection yield were ascertained.

RESULTS

A total of 21 neoplastic lesions (2 carcinomas, 4 of high-grade dysplasia and 15 of low-grade dysplasia) and 27 nondysplastic lesions were detected in 16 of the total 67 patients (70% male; median disease duration: 17 years; median age at diagnosis: 25 years; 92% aminosalicylate-treated). The dysplasia detection rate was 10.5% (7/67 patients). The dysplasia detection yield was 20.8% (10/48) for targeted biopsies and 3.5% (11/318) for nontargeted biopsies. The sensitivity and specificity for the macroscopic evaluation of neoplasia using chromoendoscopy were 48% [95% confidence interval (CI): 26%-70%] and 96% (95%CI: 93%-98%), respectively. The positive predictive and negative predictive values were 42% (95%CI: 27%-59%) and 97% (95%CI: 95%-98%), respectively. A total of 19/21 dysplastic lesions were detected in mucosa with histologic inflammation.

CONCLUSION

Chromoendoscopy seems to be of value for dysplasia surveillance of ulcerative colitis in a community hospital setting. The yield of non-targeted biopsies is negligible.

Key words: Colorectal cancer; Dysplasia; Ulcerative colitis; Surveillance; Chromoendoscopy

© The Author(s) 2018. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Patients with longstanding and extensive ulcerative colitis are at increased risk of developing colonic neoplasia and are advised to undergo regular

colonoscopic surveillance. Current clinical guidelines favour chromoendoscopy with targeted biopsies, as it detects dysplasia more accurately and thus requires fewer biopsies than white-light endoscopy. However, these recommendations are based on studies performed in advanced endoscopic units and chromoendoscopy is not routinely applied in everyday clinical practice. This prospective cohort study suggests that, although novice to chromoendoscopy, endoscopists can accurately evaluate the absence of neoplasia. The yield of nontargeted biopsies was also found to be negligible.

Klepp P, Tollisen A, Røseth A, Cvancarova Småstuen M, Andersen SN, Vatn M, Moum BA, Brackmann S. Real-life chromoendoscopy for dysplasia surveillance in ulcerative colitis. *World J Gastroenterol* 2018; 24(35): 4069-4076 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v24/i35/4069.htm> DOI: <http://dx.doi.org/10.3748/wjg.v24.i35.4069>

INTRODUCTION

Patients with extensive and long-standing ulcerative colitis (UC) carry an increased risk of developing colonic neoplastic lesions^[1]. Carcinoma in UC is thought to develop through a stepwise progression from inflammation to low-grade dysplasia and finally to carcinoma^[2]. Patients are therefore advised to undergo periodic colonoscopic surveillance, so as to detect neoplasia at an early stage^[3]. Visualization of dysplastic lesions in UC represents a challenge as they may be flat or obscured by inflammatory changes and/or pseudopolyps^[4]. Dysplasia surveillance using white-light endoscopy relies on random 4-quadrant biopsies taken every 10 cm, being a laborious and costly method^[5]. Under-sampling is common with that technique and even if the recommended 30-40 biopsies are harvested, only a fraction of the entire mucosal surface of the colon is examined^[6].

Chromoendoscopy (CE), on the other hand, uses a topical dye, which highlights mucosal abnormalities and allows for more precise biopsies^[7]. Targeted biopsies are considered superior to random biopsies of apparently unaffected mucosa, as the latter are of little additional value since they have poor diagnostic yield^[8]. Thus, recommendations for surveillance using CE are based on the assumption that CE requires fewer biopsies and is more cost effective than standard white-light endoscopy^[7,9-11]. European clinical guidelines recommend CE with targeted biopsies as the favoured technique for dysplasia surveillance^[3]. It is important to note that these guidelines are based on studies that were performed in endoscopic units with highly advanced expertise. However, in many countries, such as Norway, CE is not routinely applied for surveillance of UC patients. A retrospective multicentre study conducted over a 14-year period of CE implementation also did not show significant increase in the detection of

Table 1 Patient demographics and clinical features

| Feature | Data |
|--|-------------------------------|
| Study patients | 67 |
| Age (yr) | 40 (27-73) |
| Male sex | 46 (70) |
| Disease duration (yr) | 17 (8-51) |
| Age at diagnosis (yr) | 25 (12-59) |
| Colitis activity index score ² | 0 (0-8) |
| Primary sclerosing cholangitis | 3 (5), missing <i>n</i> = 2 |
| Colorectal cancer in first degree relative | 3 (5), missing <i>n</i> = 5 |
| Previous dysplasia in colon | 3 (5), missing <i>n</i> = 3 |
| Treatment | |
| Aminosalicylate ¹ | 58 (92), missing <i>n</i> = 3 |
| Steroids ¹ | 12 (18), missing <i>n</i> = 4 |
| Azathioprine ¹ | 4 (6) |
| Antitumour necrosis factor ¹ | 4 (6), missing <i>n</i> = 1 |

¹At time of surveillance colonoscopy and/or during past two years;

²Simple clinical colitis activity index. Data are presented as *n* (%) or median (interquartile range).

dysplastic lesions^[12].

The aim of this study was to assess the macroscopic and histologic evaluation of CE when implemented in real-life surveillance of patients with long-standing UC in a community hospital in Norway.

MATERIALS AND METHODS

Ethical considerations

The study protocol was designed according to the combined knowledge and expertise of Assistant Professor Stephan Brackmann (Akershus University Hospital), Professor Bjørn A Moum (Oslo University Hospital) and Professor Morten Vatn (University of Oslo). The study protocol was approved by the Regional Committee for Medical and Health Research Ethics (Project NO. 2010/1093). Written informed consent was collected from all subjects prior to study inclusion.

Recruitment of participants

Patients registered in the database of Lovisenberg Hospital from 1999-2013 were invited to participate in the present study if they had (1) extensive UC, documented by endoscopy at any time during the course of disease, and (2) disease duration of 8 years or more. Exclusion criteria included colectomy at any time during follow-up and poor bowel preparation (Figure 1). Demographic and clinical data were extracted from digital medical journals and by interview of the patients (Table 1).

CE

Patients underwent standard bowel preparation with sodium phosphate. CE was performed with standard definition endoscope (CF190 colonoscope; Olympus, Tokyo, Japan) and only carried out when the quality of bowel preparation was adequate (*n* = 67/68). The colonoscope was advanced to the cecum and during

the extubation each segment (cecum, ascending colon, transverse colon, descending sigmoid and rectum) was scrutinised for lesions after the spray catheter application of 0.3% indigo-carmin. Extensive colitis was defined as endoscopic inflammation proximal to the splenic flexure. Endoscopic degree of inflammation was classified according to the Mayo endoscopic score for UC^[13].

Biopsies

The location and size of all lesions identified after spray catheter application of 0.3% indigo-carmin dye were reported. Also the appearance of the lesions was classified according to terminology adapted from the Scenic Consensus^[14] as either nonpolypoid flat or elevated or polypoid pedunculated or nonpedunculated before the lesions were biopsied or removed.

In addition, after spray catheter application of 0.3% indigo-carmin dye, a minimum of one nontargeted biopsy was taken from each of the six segments (cecum, ascending, transverse and descending colon, sigmoid and rectum) to determine the extent of disease and grade of inflammation.

Independent and blind analyses of the formalin-fixed paraffin-embedded biopsies were performed by two expert gastropathologists. The histologic degree of inflammation was graded based on the histological activity index^[15]. Mucosal biopsies were classified as either negative for neoplasia, indefinite for dysplasia, or positive for low-grade dysplasia (LGD), high-grade dysplasia (HGD) or adenocarcinoma^[16]. Neoplasia was considered proximal or distal according to its anatomic location to the splenic flexure. The dysplasia detection yield was defined as the proportion of bioptic sites/lesions containing dysplasia or invasive colorectal cancer (CRC) in relation to the total number of bioptic sites/lesions. The dysplasia detection rate was defined as the proportion of patients who had at least one dysplastic lesion or invasive CRC in relation to the total number of screened patients.

Statistical analysis

The statistical methods of this study were reviewed by Milada Cvancarova Småstuen (Institute of Clinical Medicine, University of Oslo, PO Box 1122 Blindern, 0317 Oslo, Norway). All statistical analyses were carried out with the SPSS software, version 24 (IBM Corp, Armonk, NY, United States). Patient demographic characteristics were summarized as median (interquartile range) for continuous variables and as percentage of subgroup totals for categorical variables. Sensitivity and specificity were estimated with corresponding 95% confidence intervals (CIs) that were calculated using the exact binomial distribution.

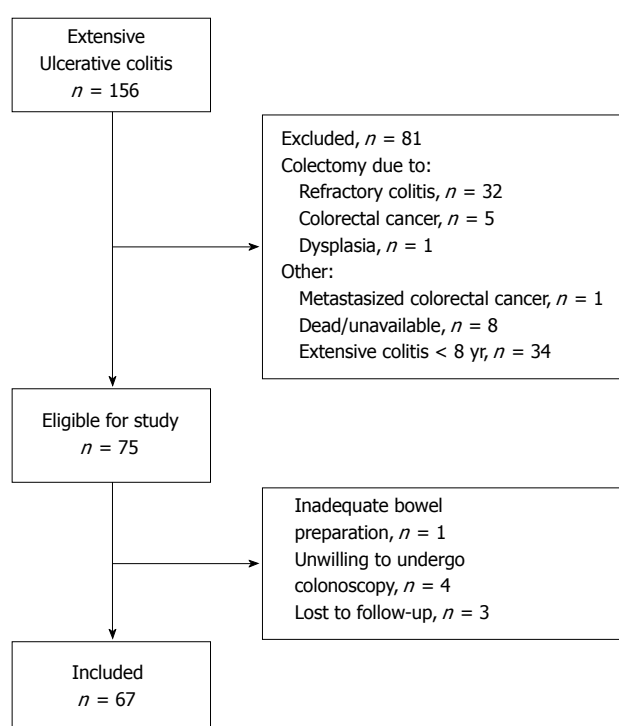
RESULTS

CE was performed in 67 patients with extensive UC. A

Table 2 Histologic diagnosis of the seven neoplastic lesions detected among the 67 total patients with long-standing and extensive ulcerative colitis

| Sex | Age (yr) | LGD | | HGD | Adenocarcinoma | Total |
|--------|----------|-----------------|--------------------|-----------------|-----------------|-------|
| | | Targeted biopsy | Nontargeted biopsy | Targeted biopsy | Targeted biopsy | |
| Male | 34 | 1 | 7 | 4 | 1 ¹ | 13 |
| Male | 67 | | | | 1 ² | 1 |
| Male | 49 | 1 | 1 | | | 2 |
| Male | 33 | 1 | | | | 1 |
| Female | 36 | 1 | | | | 1 |
| Male | 44 | | 1 | | | 1 |
| Female | 52 | | 2 | | | 2 |
| Total | | 4 | 11 | 4 | 2 | 21 |

¹Adenocarcinoma stage T3N1M0 in patient with primary sclerosing cholangitis; ²Adenocarcinoma stage T2N0M0. No neoplasia was found in biopsies despite high suspicion of malignancy at endoscopy. Adenocarcinoma was subsequently verified in the resected surgical specimen. LGD: Low-grade dysplasia; HGD: High-grade dysplasia.

**Figure 1** Flowchart of patient inclusion for this study.

total of 21 neoplastic lesions were detected in 7 of the 67 patients, including 10 (comprised of 2 CRC, 4 HGD and 4 LGD) identified by targeted biopsies and 11 (all LGD) by nontargeted biopsies.

Dysplasia detection rate

Neoplasia was detected in 7 of the total 67 patients, giving a dysplasia detection rate of 10.5%. In 4, neoplasia was detected from both targeted and nontargeted biopsies. In 2, dysplasia was detected by nontargeted biopsies alone. In 1, adenocarcinoma was diagnosed after partial colonic resection.

Dysplasia detection yield

A total of 48 lesions were visualised in 16 of the total 67 patients. The median number of lesions per patient

was 1 (range: 0-6). The distribution and findings from endoscopic and histologic evaluations of the lesions are described in detail in Figure 2 and Tables 2 and 3. Ten of the visualised lesions harboured neoplasia, resulting in a dysplasia detection yield of 20.8% for targeted biopsies. Among the 318 nontargeted biopsies, 11 harboured LGD, resulting in a dysplasia detection yield of 3.5% for nontargeted biopsies.

Macroscopic evaluation

Correct classification by the endoscopists was achieved for 307 of the 345 nondysplastic sites/lesions and 10 of the 21 dysplastic sites/lesions. On the other hand, 11 of the 21 dysplastic lesions were assessed as nondysplasia, whereas 38 of the 345 nondysplastic sites/lesions were assessed as dysplasia. As a result, the sensitivity and specificity for the macroscopic evaluation of neoplasia using CE were 48% (95%CI: 26%-70%) and 96% (95%CI: 93%-98%), respectively. The positive predictive value was 42% (95%CI: 27%-59%) and the negative predictive value (NPV) was 97% (95%CI: 95%-98%).

Follow-up of patients with colonic neoplasia

In 2 of the 7 patients with LGD, the dysplasia was detected solely by nontargeted biopsies taken during a CE described as macroscopically normal. Follow-up with colonoscopy neither confirmed nor revealed any further dysplasia for either patient. In another 2 of the 7 patients, the LGD was detected solely by targeted biopsies. In yet another 2 of the 7 patients, nontargeted biopsies confirmed a field effect by detecting LGD when dysplastic lesions were identified elsewhere in the colorectum by targeted biopsies; during intensified follow-up colonoscopy, no further dysplasia was detected after 2.5 years follow-up (range: 2-5 years) in these patients.

In 1 of the 7 patients with neoplasia, nontargeted biopsies showed multifocal fields of LGD synchronous with targeted biopsies that showed multifocal lesions with HGD and adenocarcinoma. The patient had primary sclerosing cholangitis and proctocolectomy

Table 3 Morphology and histology findings for the 16 bioptic sites of the 67 total patients with long-standing and extensive ulcerative colitis

| Morphology | Histology | n |
|---------------------------------|----------------|----------------|
| Targeted biopsy | | |
| Nonpolypoid | | |
| Flat lesion | No neoplasia | 26 |
| | LGD | 2 |
| | HGD | 1 ¹ |
| Superficial elevated | No neoplasia | 10 |
| | HGD | 1 ¹ |
| | Adenocarcinoma | 1 |
| Polypoid | | |
| Pedunculated | No neoplasia | 1 |
| | LGD | 1 |
| Nonpedunculated | LGD | 1 |
| Sessile with central ulceration | HGD | 2 ¹ |
| Sessile | Adenocarcinoma | 1 ¹ |
| | IND | 1 |
| Nontargeted biopsy | | |
| | No neoplasia | 307 |
| | LGD | 11 |
| Total | | 366 |

¹Concomitant primary sclerosing cholangitis. HGD: High-grade dysplasia; IND: Indefinite dysplasia; LGD: Low-grade dysplasia.

was performed. Finally, adenocarcinoma was detected after partial resection of the colon in 1 of the 7 patients for who endoscopy had raised suspicion of malignancy, whereas targeted biopsies of this area were normal on two consecutive colonoscopies. After surgery, no further neoplasia was detected during 3 years of intensified follow-up colonoscopies.

Mucosal inflammation

No signs of histologic inflammation were recorded in 93 of the 366 bioptic sites. A total of 237 had Mayo grade 0-1 and 39 had Mayo grade 2-3. The presence of neoplasia in relation to histologic inflammatory changes is described in detail in Table 4.

Schedule of surveillance colonoscopy

The median time from the prior "prestudy" surveillance colonoscopy ($n = 61/67$) until the next scheduled colonoscopy was 24 mo (range: 0-96 mo). The median time from the prior "prestudy" surveillance colonoscopy ($n = 66/67$) until the study CE was 26 mo (range: 1-105 mo).

DISCUSSION

This prospective cohort study performed in a community hospital suggests that, although novice to CE, endoscopists were able to accurately evaluate the absence of neoplasia during real-life surveillance of patients with UC. Neoplasia was detected by targeted biopsies in 5 of the 67 total patients, of whom 2 had a field effect confirmed by nontargeted biopsies. Two additional patients were diagnosed with LGD in the colon

by nontargeted biopsies alone. The neoplasia detection rate for the 7 of the 67 total patients in the present study is similar to that found in studies performed in tertiary referral centres (11.2%). It is important to note, however, that the present study was conducted in a community hospital in which patients may present with a less aggressive UC than seen in advanced units.

The neoplasia detection yield of the present study was 20.8%, which is lower than the average rate of 14% found by Mooiweer *et al.*^[12] in several prior randomized trials. The endoscopists in our study were able to accurately rule-out neoplasia (NPV = 97%); thus, when the endoscopists evaluated the lesion as benign, the probability of dysplasia was minimal (3%). These results are in line with a recent prospective multicentre cohort study in which both CE novice endoscopists and CE expert endoscopists evaluated lesions, and had a high NPV^[17]. That same study found a sensitivity of 70% for CE, which is lower than the pooled sensitivity of 91% reported from a recent meta-analysis^[17,18]. In the present study, the sensitivity for the detection of LGD by CE was modest, which could be related to the endoscopists' lack of prior CE experience.

Alternatively, these results support the presence of "invisible" dysplasia. In our cohort, "invisible" dysplasia was rare in the absence of dysplastic lesions elsewhere in the colon, similar to findings reported by Matsumoto *et al.*^[9,19] and underlining the concept of field cancerization in UC^[9,19]. The results must, however, be evaluated with caution due to the size of the study sample and the low observed rate of cases.

The clinical importance of dysplasia detected through random biopsies is debatable. In the present study, the dysplasia detection yield was 3.5% for nontargeted biopsies compared to a 20.8% for targeted biopsies. The nontargeted biopsies were primarily taken not to detect neoplasia but to evaluate the grade of mucosal inflammation. In line with previous studies, the low dysplasia yield of nontargeted biopsies leads to questions about their clinical value^[7,8,17,20,21]. Also, the follow-up of the patients in which LGD was detected by nontargeted biopsy alone did not reveal any further dysplasia. However, a recent study has suggested that despite a low bioptic neoplasia yield, nontargeted biopsies are advisable in patients with inflammatory bowel disease and related high risk of CRC^[21].

Clinical guidelines recommend the first surveillance colonoscopy to be performed between 8-10 years after the diagnosis of UC, with ensuing colonoscopies based on individual risk. In our cohort, the median time until the next scheduled colonoscopy was 24 mo, which is in accordance with guidelines^[3].

The visualisation of small lesions harbouring dysplasia may have been hampered by inflammation surrounding multifocal lesions. However, the minimal level of inflammatory changes in those patients in who dysplasia was diagnosed by nontargeted biopsies only did not likely impede the detection.

Table 4 Histologic grade of inflammation in the biopsies taken from all 67 patients

| | Grade of inflammation | | | | | Total |
|------------------|-----------------------|--------|--------|--------|-----------------------------------|-------|
| | Mayo 0 ¹ | Mayo 1 | Mayo 2 | Mayo 3 | No signs of previous inflammation | |
| No dysplasia/IND | 133 | 83 | 33 | 3 | 93 | 345 |
| LGD | 3 | 12 | 0 | 0 | 0 | 15 |
| HGD | 0 | 2 | 2 | 0 | 0 | 4 |
| CRC | 0 | 1 | 1 | 0 | 0 | 2 |
| Total | 136 | 98 | 36 | 3 | 93 | 366 |

¹Inactive colitis. CRC: Colorectal cancer; HGD: High-grade dysplasia; IND: Indefinite dysplasia; LGD: Low-grade dysplasia.

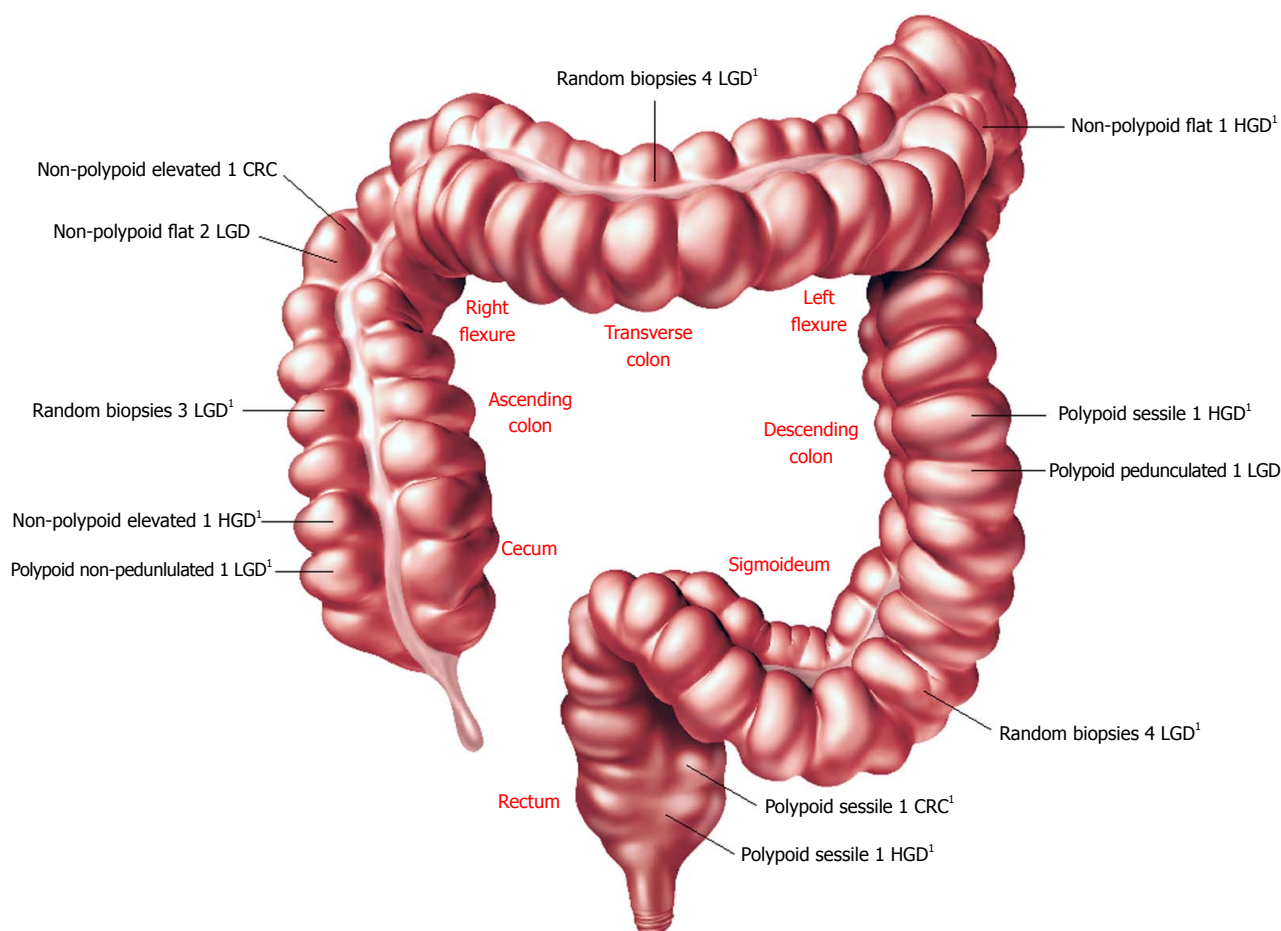


Figure 2 Distribution and findings of endoscopic and histologic evaluation of the 21 total neoplastic lesions found in this study. ¹Lesions detected in patient with known primary sclerosing cholangitis.

In the present study, current or previous inflammatory changes were found to be present around all dysplastic lesions, including for nontargeted biopsies harbouring lesions with LGD. These results support the findings of Watanabe *et al.*^[22], who suggested that random biopsies may be omitted in the absence of previous or current inflammation.

We recognize that the present study has several limitations. The adenoma detection rate of the endoscopists is not currently implemented in Norway and therefore not available for the endoscopists in the present study. Both endoscopists had however substantial experience in non-CE endoscopy. The present study reflects the everyday

clinical world in this location. Each CE was performed with standard and not high-definition endoscopes, which may have affected the detection of lesions. The prospective cohort design of the study minimizes patient selection bias; however, the sample size is moderate, although considerable effort was spent on the inclusion of patients. Patients may have been reluctant to undergo colonoscopy. Low compliance rates for surveillance endoscopy have previously been described, although the reasons remain unclear^[23]. Additionally, although all the patients in the sample carry an increased risk of colonic neoplasia, the low observed rate of neoplasia resulted in wide CIs around sensitivity estimates for the detection of

dysplastic lesions.

Despite the limitations outlined above, the results of the present study are thought to reflect the real-life scenario of dysplasia surveillance in UC in a community-based hospital in Norway, which could represent the typical setting in similar hospitals in Europe where CE is not routinely applied.

In conclusion, the present study suggests that, although lacking in previous CE expertise, the endoscopists were able to accurately evaluate the absence of neoplasia. The yield of nontargeted biopsies with LGD was negligible, and LGD appears to be present in mucosa with signs of histologic inflammation. Finally, dysplasia in endoscopically unsuspicious appearing mucosa seems to occur mostly when visible neoplasia is diagnosed elsewhere in the colon. Although further larger studies are needed, CE seems to be of value for surveillance of neoplasia in UC in a community hospital setting.

ARTICLE HIGHLIGHTS

Research background

Patients with longstanding and extensive ulcerative colitis carry an increased risk of developing colonic neoplasia and are advised to undergo regular colonoscopic surveillance.

Research motivation

The current clinical guidelines favour chromoendoscopy with targeted biopsies for dysplasia surveillance of ulcerative colitis. These recommendations, however, are based on studies performed in advanced endoscopic units and chromoendoscopy is not routinely applied in everyday clinical practice.

Research objectives

Our aim was to evaluate chromoendoscopy for real-life dysplasia surveillance for cases of long-standing ulcerative colitis in a community hospital.

Research methods

Patients with extensive ulcerative colitis, with disease duration of more than 8 years, were prospectively included in this single cohort study. The chromoendoscopies were performed by two expert endoscopists novice to the method. Lesions were evaluated macroscopically and removed and/or biopsied. Nontargeted biopsies were also taken from each segment of the colon.

Research results

A total of 21 neoplastic lesions (consisting of 2 carcinomas, 4 high-grade dysplasias and 15 low-grade dysplasias) and 27 nondysplastic lesions were detected in 16 of the 67 total patients included in the study. The dysplasia detection rate was 10.5% (for 7 of the 67 patients). The dysplasia detection yield was 20.8% (10/48) for targeted biopsies and 3.5% (11/318) for nontargeted biopsies. The endoscopists accurately evaluated the absence of neoplasia (specificity of 96%, with 95% confidence interval of 93-98; and a negative predictive value of 97%, with 95% confidence interval of 95%-98%).

Research conclusions

Although novice to chromoendoscopy, the endoscopists in this Norwegian community hospital accurately evaluated the absence of neoplasia. In addition, the yield of nontargeted biopsies was negligible.

Research perspectives

Chromoendoscopy appears to be of value for dysplasia surveillance for cases of long-standing ulcerative colitis who are treated in a community hospital setting in which endoscopists are novice to the technique.

ACKNOWLEDGMENTS

The authors thank the staff at the Unger-Vetlesen Research Institute, Lovisenberg Diaconal Hospital and Lars Gustav Lyckander at the Department of Pathology, Akershus University Hospital.

REFERENCES

- 1 **Rubin DT**, Huo D, Kinnucan JA, Sedrak MS, McCullom NE, Bunnag AP, Raun-Royer EP, Cohen RD, Hanauer SB, Hart J, Turner JR. Inflammation is an independent risk factor for colonic neoplasia in patients with ulcerative colitis: a case-control study. *Clin Gastroenterol Hepatol* 2013; **11**: 1601-1608.e1-e4 [PMID: 23872237 DOI: 10.1016/j.cgh.2013.06.023]
- 2 **Ullman TA**, Itzkowitz SH. Intestinal inflammation and cancer. *Gastroenterology* 2011; **140**: 1807-1816 [PMID: 21530747 DOI: 10.1053/j.gastro.2011.01.057]
- 3 **Magro F**, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, Burisch J, Gecse KB, Hart AL, Hindryckx P, Langner C, Limdi JK, Pellino G, Zagorowicz E, Raine T, Harbord M, Rieder F; European Crohn's and Colitis Organisation [ECCO]. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileal-anal Pouch Disorders. *J Crohns Colitis* 2017; **11**: 649-670 [PMID: 28158501 DOI: 10.1093/ecco-jcc/jjx008]
- 4 **Velayos FS**, Loftus EV Jr, Jess T, Harmsen WS, Bida J, Zinsmeister AR, Tremaine WJ, Sandborn WJ. Predictive and protective factors associated with colorectal cancer in ulcerative colitis: A case-control study. *Gastroenterology* 2006; **130**: 1941-1949 [PMID: 16762617 DOI: 10.1053/j.gastro.2006.03.028]
- 5 **Annese V**, Beaugier L, Egan L, Biancone L, Bolling C, Brandts C, Dierickx D, Dummer R, Fiorino G, Gornet JM, Higgins P, Katsanos KH, Nissen L, Pellino G, Rogler G, Scaldaferrì F, Szymanska E, Eliakim R; ECCO. European Evidence-based Consensus: Inflammatory Bowel Disease and Malignancies. *J Crohns Colitis* 2015; **9**: 945-965 [PMID: 26294789 DOI: 10.1093/ecco-jcc/jjv141]
- 6 **Eaden JA**, Ward BA, Mayberry JF. How gastroenterologists screen for colonic cancer in ulcerative colitis: an analysis of performance. *Gastrointest Endosc* 2000; **51**: 123-128 [PMID: 10650251]
- 7 **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: 14724160 DOI: 10.1136/gut.2003.016386]
- 8 **van den Broek FJ**, Stokkers PC, Reitsma JB, Boltjes RP, Ponsioen CY, Fockens P, Dekker E. Random biopsies taken during colonoscopic surveillance of patients with longstanding ulcerative colitis: low yield and absence of clinical consequences. *Am J Gastroenterol* 2014; **109**: 715-722 [PMID: 21427710 DOI: 10.1038/ajg.2011.93]
- 9 **Matsumoto T**, Nakamura S, Jo Y, Yao T, Iida M. Chromoscopy might improve diagnostic accuracy in cancer surveillance for ulcerative colitis. *Am J Gastroenterol* 2003; **98**: 1827-1833 [PMID: 12907339 DOI: 10.1111/j.1572-0241.2003.07580.x]
- 10 **Marion JF**, Waye JD, Israel Y, Present DH, Suprun M, Bodian C, Harpaz N, Chapman M, Itzkowitz S, Abreu MT, Ullman TA, McBride RB, Aisenberg J, Mayer L; Chromoendoscopy Study Group at Mount Sinai School of Medicine. Chromoendoscopy Is More Effective Than Standard Colonoscopy in Detecting Dysplasia During Long-term Surveillance of Patients With Colitis. *Clin Gastroenterol Hepatol* 2016; **14**: 713-719 [PMID: 26656297 DOI: 10.1016/j.cgh.2015.11.011]
- 11 **Konijeti GG**, Shrive MG, Ananthakrishnan AN, Chan AT. Cost-effectiveness analysis of chromoendoscopy for colorectal cancer surveillance in patients with ulcerative colitis. *Gastrointest Endosc* 2014; **79**: 455-465 [PMID: 24262637 DOI: 10.1016/j.gie.2013.10.026]

- 12 **Mooiweer E**, van der Meulen-de Jong AE, Ponsioen CY, Fidder HH, Siersema PD, Dekker E, Oldenburg B. Chromoendoscopy for Surveillance in Inflammatory Bowel Disease Does Not Increase Neoplasia Detection Compared With Conventional Colonoscopy With Random Biopsies: Results From a Large Retrospective Study. *Am J Gastroenterol* 2015; **110**: 1014-1021 [PMID: 25823770 DOI: 10.1038/ajg.2015.63]
- 13 **Schroeder KW**, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987; **317**: 1625-1629 [PMID: 3317057 DOI: 10.1056/NEJM198712243172603]
- 14 **Laine L**, Kaltenbach T, Barkun A, McQuaid KR, Subramanian V, Soetikno R; SCENIC Guideline Development Panel. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. *Gastrointest Endosc* 2015; **81**: 489-501.e26 [PMID: 25708752 DOI: 10.1016/j.gie.2014.12.009]
- 15 **Gupta RB**, Harpaz N, Itzkowitz S, Hossain S, Matula S, Kornbluth A, Bodian C, Ullman T. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. *Gastroenterology* 2007; **133**: 1099-1105; quiz 1340-1341 [PMID: 17919486 DOI: 10.1053/j.gastro.2007.08.001]
- 16 **Riddell RH**, Goldman H, Ransohoff DF, Appelman HD, Fenoglio CM, Haggitt RC, Ahren C, Correa P, Hamilton SR, Morson BC. Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. *Hum Pathol* 1983; **14**: 931-968 [PMID: 6629368 DOI: 10.1016/S0046-8177(83)80175-0]
- 17 **Carballal S**, Maisterra S, López-Serrano A, Gimeno-García AZ, Vera MI, Marín-Garbriel JC, Díaz-Tasende J, Márquez L, Álvarez MA, Hernández L, De Castro L, Gordillo J, Puig I, Vega P, Bustamante-Balén M, Acevedo J, Peñas B, López-Cerón M, Ricart E, Cuatrecasas M, Jimeno M, Pellisé M; EndoCAR group of the Spanish Gastroenterological Association and Spanish Digestive Endoscopy Society. Real-life chromoendoscopy for neoplasia detection and characterisation in long-standing IBD. *Gut* 2018; **67**: 70-78 [PMID: 27612488 DOI: 10.1136/gutjnl-2016-312332]
- 18 **Wu L**, Li P, Wu J, Cao Y, Gao F. The diagnostic accuracy of chromoendoscopy for dysplasia in ulcerative colitis: meta-analysis of six randomized controlled trials. *Colorectal Dis* 2012; **14**: 416-420 [PMID: 21073646 DOI: 10.1111/j.1463-1318.2010.02505.x]
- 19 **Leedham SJ**, Graham TA, Oukrif D, McDonald SA, Rodriguez-Justo M, Harrison RF, Shepherd NA, Novelli MR, Jankowski JA, Wright NA. Clonality, founder mutations, and field cancerization in human ulcerative colitis-associated neoplasia. *Gastroenterology* 2009; **136**: 542-550.e6 [PMID: 19103203 DOI: 10.1053/j.gastro.2008.10.086]
- 20 **Marion JF**, Wayne JD, Present DH, Israel Y, Bodian C, Harpaz N, Chapman M, Itzkowitz S, Steinlauf AF, Abreu MT, Ullman TA, Aisenberg J, Mayer L; Chromoendoscopy Study Group at Mount Sinai School of Medicine. Chromoendoscopy-targeted biopsies are superior to standard colonoscopic surveillance for detecting dysplasia in inflammatory bowel disease patients: a prospective endoscopic trial. *Am J Gastroenterol* 2008; **103**: 2342-2349 [PMID: 18844620 DOI: 10.1111/j.1572-0241.2008.01934.x]
- 21 **Moussata D**, Allez M, Cazals-Hatem D, Treton X, Laharie D, Reimund JM, Bertheau P, Bourreille A, Lavergne-Slove A, Brixi H, Branche J, Gornet JM, Stefanescu C, Moreau J, Marteau P, Pelletier AL, Carbonnel F, Seksik P, Simon M, Fléjou JF, Colombel JF, Charlois AL, Roblin X, Nancey S, Bouhnik Y, Berger F, Flourié B; the GETAID. Are random biopsies still useful for the detection of neoplasia in patients with IBD undergoing surveillance colonoscopy with chromoendoscopy? *Gut* 2018; **67**: 616-624 [PMID: 28115492 DOI: 10.1136/gutjnl-2016-311892]
- 22 **Watanabe T**, Ajioka Y, Mitsuyama K, Watanabe K, Hanai H, Nakase H, Kunisaki R, Matsuda K, Iwakiri R, Hida N, Tanaka S, Takeuchi Y, Ohtsuka K, Murakami K, Kobayashi K, Iwao Y, Nagahori M, Iizuka B, Hata K, Igarashi M, Hirata I, Kudo SE, Matsumoto T, Ueno F, Watanabe G, Ikegami M, Ito Y, Oba K, Inoue E, Tomotsugu N, Takebayashi T, Sugihara K, Suzuki Y, Watanabe M, Hibi T. Comparison of Targeted vs Random Biopsies for Surveillance of Ulcerative Colitis-Associated Colorectal Cancer. *Gastroenterology* 2016; **151**: 1122-1130 [PMID: 27523980 DOI: 10.1053/j.gastro.2016.08.002]
- 23 **Vienne A**, Simon T, Cosnes J, Baudry C, Bouhnik Y, Soulé JC, Chaussade S, Marteau P, Jian R, Delchier JC, Coffin B, Admane H, Carrat F, Drouet E, Beaugerie L. Low prevalence of colonoscopic surveillance of inflammatory bowel disease patients with longstanding extensive colitis: a clinical practice survey nested in the CESAME cohort. *Aliment Pharmacol Ther* 2011; **34**: 188-195 [PMID: 21615760 DOI: 10.1111/j.1365-2036.2011.04711]

P- Reviewer: Hiraoka S, Luo H, Tandon RK, Tang ZP
S- Editor: Wang XJ **L- Editor:** A **E- Editor:** Huang Y





Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>



ISSN 1007-9327

