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Review Article

Surveillance and management of colorectal dysplasia and cancer in inflammatory bowel disease: Current practice and future perspectives

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ABSTRACT

Patients with inflammatory bowel disease (IBD) are at increased risk of developing colorectal cancer (CRC). Current guidelines recommend frequent surveillance colonoscopies for patients with at least left-sided ulcerative colitis, or Crohn's disease involving more than 30% of the colon. Surveillance allows for early detection and treatment of colorectal dysplasia and cancer. The first colonoscopy should be performed 8 to 10 years after onset of disease symptoms. European and British guidelines employ a risk-stratification algorithm that assigns patients to surveillance intervals of one, three or five years, whereas American guidelines recommend to perform surveillance every 1 to 3 years based on the (combined) presence of risk factors. Patients with concomitant primary sclerosing cholangitis are at an additionally increased risk, and should undergo annual surveillance starting immediately after the diagnosis. The current practice of surveillance is based on limited evidence, is resource intensive and cannot preclude the occurrence of interval carcinomas. Fortunately, advances in endoscopic techniques for mucosal visualisation, along with better control of inflammation, have resulted in a declining incidence of CRC in patients with IBD. Furthermore, advanced endoscopic resection techniques can be expected to result in a shift from surgical to endoscopic management of dysplastic lesions. In this review, we provide an up-to-date overview of colitis-associated CRC pathophysiology, epidemiology, surveillance practices, and management of dysplasia.

1. Introduction

Almost a century ago, Crohn and Rosenberg described the first case of ulcerative colitis (UC) complicated by colorectal carcinoma (CRC). [1] Nowadays, it is widely recognised that patients with colonic inflammatory bowel disease (IBD), including UC and Crohn's disease (CD), are at increased risk of CRC and therefore these patients are enrolled in surveillance programs. [2-8] Endoscopic surveillance aims to detect and remove precursor lesions or early-stage CRC, and has been linked to a decreased risk of CRC and corresponding mortality based on retrospective data. [9]

The development of novel endoscopic technologies has had an enormous impact on endoscopy practices. High-definition endoscopes allow for detailed visualisation of the colonic mucosa, and novel resection techniques enable endoscopic treatment of lesions that previously had to be removed surgically. [10] This technological progress, along with the expanding therapeutic armamentarium to control inflammation, [11, 12] likely explains why the incidence of colitis-associated CRC has declined over time. [3]

In the light of these developments, this review aims to provide an up-to-date overview on the pathophysiology, epidemiology, surveillance strategies and management of colitis-associated dysplasia and cancer. Furthermore, we will highlight several areas of interest for further research.

Abbreviations: 5-ASA, 5-aminosalicilyc acid; CD, Crohn's disease; CRC, Colorectal cancer; EMR, Endoscopic mucosal resection; ESD, Endoscopic submucosal dissection; HD, High-definition; HGD, High-grade dysplasia; IBD, Inflammatory bowel disease; LGD, Low-grade dysplasia; pks, polyketide nonribosomal peptide synthase operon; PSC, Primary sclerosing cholangitis; RCT, Randomised controlled trial; TNF-alpha, Tumour necrosis factor-alpha; UC, Ulcerative colitis; UDCA, Ursodeoxycholic acid.

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2. Pathophysiology

According to the widely accepted *adenoma-carcinoma sequence* paradigm, most cases of sporadic CRC develop from adenomatous polyps over a long period of time. [13] Colitis-associated CRC is thought to develop through several stages of precursor lesions as well, from inflamed but non-dysplastic epithelium to low-grade dysplasia (LGD), high-grade dysplasia (HGD) and finally CRC. [14, 15] Here, chronic inflammation is thought to be the main driver of tumourigenesis. [14] Indeed, endoscopic or histologic inflammation, and extensive disease are well-known independent risk factors for colorectal dysplasia and cancer in IBD. [16, 17]

A unique feature of the pathogenesis of colitis-associated CRC is that chronic inflammation leads to a 'field defect' of damaged DNA in colonic epithelial cells, rather than unifocal aberrant clones. [14] Small genomic alterations may be present throughout the (entire) colon affected by colitis in normally appearing, non-dysplastic mucosa. [18] From these areas, dysplastic lesions arise, which are usually endoscopically visible, using current high-definition endoscopes. [19] This field defect or 'field cancerisation' explains why dysplasia in IBD is often multifocal. [19-21]

At a genetic level, in line with sporadic CRC, most colitis-associated CRCs develop through the chromosomal instability pathway as opposed to the microsatellite instability pathway (i.e. malfunctioning of DNA mismatch repair genes, involved in Lynch syndrome). [14, 22, 23] The chromosomal instability pathway manifests by copy number alterations of chromosomes or parts of chromosomes (i.e. aneuploidy) and includes changes to the APC, TP53 and K-RAS genes, [14] among others. It is thought that these changes occur in a different sequence in colitis-associated versus sporadic CRC. For example, APC mutations are more frequent in precursors lesions of sporadic CRC (sporadic adenomas), [23] while colitis-associated precursor lesions usually harbour TP53 mutations. [24, 25] This differential sequence may explain why colitis-associated dysplasia can be morphologically distinct from sporadic adenomas, as it is often non-polypoid. [20, 21]

The gut microbiome differs between IBD patients and healthy individuals, [26] and this has recently been linked to the increased CRC risk in patients with IBD. [27] A specific strain of *Escherichia Coli* (polyketide non-ribosomal peptide synthase operon [pks] positive strain) has a twofold higher prevalence in IBD patients as compared to healthy individuals. [27] This pks-positive *Escherichia Coli* strain produces a toxin (colibactin) that damages DNA and induces a specific signature of mutations (including mutations in the APC gene and genes involved in the TP53-axis, among others) in intestinal organoids. [28,29] These preliminary findings might, in the future, lead to new targets for preventive strategies.

Finally, it should be noted that patients with IBD may also develop sporadic adenomas. Since the prognosis differs for colitis-associated dysplasia versus sporadic adenoma in IBD patients, [30] various efforts have been made to identify endoscopic or histopathological characteristics that can help making this distinction. Currently, the distinction is based on lesion morphology, presence of multifocal dysplasia, and whether the lesion is located in an area previously affected by inflammation.

3. Epidemiology

3.1. Excess risk of CRC in patients with IBD

Patients with IBD are at an 1.4 to 2.2 fold increased risk of CRC compared with the general population. [3, 31-33] Furthermore, CRC-related survival is lower among patients with IBD, even after adjustment for tumour stage at diagnosis. [32-34] Thus, both a higher incidence of CRC as well as worse clinical outcomes of colitis-associated CRC contribute to an overall increased rate of CRC-related mortality in patients with IBD. [32, 33]

The incidence of IBD-CRC is considerably higher in hospital-based studies as compared to population-based studies (1.7-3.0 per 1,000 patient-years and 0.8-1.3 per 1,000 patient-years, respectively). [31-33, 35-37] Cohort studies of patients undergoing surveillance report the highest IBD-CRC incidences (3.1-4.7 per 1,000 patient-years). [30, 38] Beaugerie's landmark study showed that IBD patients with a disease duration of more than ten years and involvement of more than half of the colonic mucosa are at a 5.2-fold (UC) and 9.0-fold (CD) increased risk of CRC compared with the general population. In contrast, patients in whom such long-standing, extensive colitis was not present had a similar CRC risk as non-IBD controls. [31]

Interestingly, the excess risk of CRC in patients with IBD has been found to decline over time in most regions where this has been examined, [3, 32] but not all. [3, 35] This decline may be explained by advances in surveillance techniques and improved management of inflammation. [2, 3] Of note, results from the longest-running surveillance cohort in patients with UC initially indicated a decreasing CRC incidence, but subsequently reported an increase in early CRC. The authors attributed this phenomenon to a shift from managing dysplasia surgically (i.e. colectomy) to endoscopic resection. [30] Reassuringly, the incidence of advanced CRC had continued to decline in the last decade.

3.2. Risk factors

Risk factors for HGD and CRC combined ('advanced colorectal neoplasia', a commonly used composite endpoint in studies) in patients with IBD include extensive colonic disease, presence of post-inflammatory polyps, colonic strictures and severity of histologic inflammation. [17] These factors are all closely related to the cumulative inflammatory burden, [16] and underpin the central role of inflammation in the pathogenesis of colitis-associated CRC. The main challenge therefore, is to create a pragmatic score for cumulative inflammation (either based on histology or endoscopy), that can be readily implemented in routine practice.

In addition to the abovementioned phenotypic features related to inflammation, primary sclerosing cholangitis (PSC) is a very strong risk factor for HGD and CRC in patients with IBD as well. [17, 39] PSC is a chronic progressive cholestatic liver disease leading to biliary inflammation and fibrosis, [39] that is exceedingly rare in the general population, but is present in 3-5% of patients with IBD (mainly UC patients). [30, 40] Similar to sporadic CRC, older age, a positive family history of CRC and male sex also increase the risk of colitis-associated HGD and CRC. [17] Moreover, IBD patients with prior indefinite dysplasia or LGD are also at increased risk of HGD and CRC. [17] The latter may be explained by various factors, including local recurrence (inadequate resections), missed synchronous lesions, or the aforementioned "field defect" of damaged DNA that extends beyond the dysplastic lesion. Notably, aneuploidy in biopsies from normally appearing mucosa may indicate a field defect and is indeed associated with a more than fivefold increased risk of HGD or CRC. [17]

4. Surveillance

4.1. Surveillance strategies

Leading guidelines recommend to perform surveillance in patients with colonic IBD. A first surveillance colonoscopy should be scheduled in all patients with colonic IBD either 8 to 10 years after onset of symptoms. [4-8] Continued surveillance is recommended if the colonic involvement exceeds proctitis (UC) or is more than 30% (CD). European and British guidelines stratify patients in one of three risk categories (high, intermediate, or low risk group) with surveillance intervals ranging from annually to every five years (Fig. 1). [4, 5] American guidelines recommend to perform surveillance every 1 to 3 years and to consider the (combined) presence of risk factors when determining the next surveillance interval. [6-8] Importantly, IBD patients with

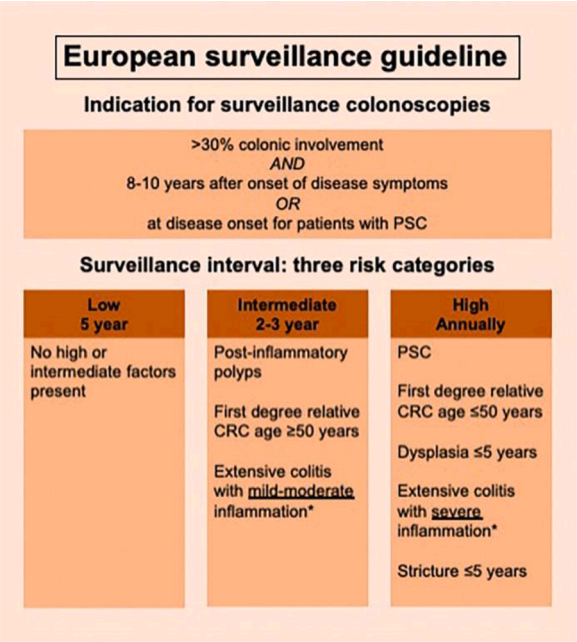

Fig. 1. Surveillance strategy of the European Crohn's and Colitis Organisation (ECCO) [4]

* Presence of inflammation is based on endoscopic or histologic inflammation. CRC=colorectal cancer, PSC=primary sclerosing cholangitis.

concomitant PSC are a distinct category. For these patients, all guidelines recommend annual surveillance, starting immediately after the diagnosis because of the strongly increased CRC risk in patients with PSC. [4-8, 17]

The (cost)effectiveness of the algorithms recommended in current guidelines has never been investigated prospectively and the available evidence is insufficient to objectively define optimal, individualised surveillance intervals. As a result, current surveillance regimens undoubtedly lead to overutilisation of health care resources, as most IBD patients will never develop CRC. This is underscored by a previous cost-effectiveness modelling study that found a risk-stratification approach for surveillance to be more cost-effective than annual or biannual surveillance. [41] Meanwhile, 30% of CRC cases in IBD are missed during surveillance and can therefore be classified as interval carcinomas. [42] Furthermore, half of the CRCs diagnosed in patients with IBD who underwent a colonoscopy in the past five years, can be attributed to a previously missed lesion, despite adequate procedural quality measures. [37] These findings highlight the need for an evidence-based systematic approach to identify patients with IBD in whom surveillance is indicated, [35, 43, 44] as well as the importance of optimising surveillance techniques to reduce the risk of missed lesions.

4.2. Surveillance technique

Colonoscopy is the gold standard for CRC surveillance in IBD patients. Optimal bowel preparation and disease remission are absolute requirements for adequate surveillance. [42, 45] Present guidelines recommend to perform surveillance colonoscopies employing chromoendoscopy. [4-6, 8, 46] Chromoendoscopy creates enhanced images by directly spraying dye on the colonic mucosa during endoscopy (Fig. 2). Lichtenstein et. al. published an educational video that illustrates this technique. [47] Downsides of chromoendoscopy are that this technique prolongs procedure time, requires additional training, and may be perceived as impractical by endoscopists. [48] It can be questioned whether the advent of high definition (HD) endoscopy has made chromoendoscopy redundant. Previous meta-analyses including only randomised controlled trials (RCT) reported similar dysplasia detection rates with and without chromoendoscopy in patients with IBD. [48-50] In contrast, superiority of surveillance using chromoendoscopy was reported in a recent well-conducted RCT from Sweden (Supplementary Table 1 provides summary data of these RCTs). [51] Nowadays, most guidelines still recommend chromoendoscopy, but also state that white light endoscopy using HD endoscopes is a good alternative.

The role of random biopsies, four biopsies every ten centimetres, in surveillance colonoscopies, using HD endoscopes, has also become unclear. [46] The rationale for random biopsies is that they may detect dysplastic lesions that cannot be identified endoscopically. As with chromoendoscopy, taking random biopsies prolongs procedure time and additionally adds costs of histopathologic evaluation. In this era of HD endoscopes, the neoplastic yield of *only* random biopsies in IBD patients in the setting of surveillance is quite low, 1.2-3.0% per-colonoscopy and 0.09-0.2% per biopsy. [51, 52] Non-inferiority in neoplasia detection was reported for surveillance with *only* targeted biopsies versus target and random biopsies in a RCT study, although no data on long-term outcomes were reported. [53] The yield of random biopsies is higher in patients with concomitant PSC (3.7% per-colonoscopy and 0.3% per biopsy), [51, 52, 54, 55] prior dysplasia, or a tubular colon. [52] The added value of random biopsies in these high-risk patients should be balanced against additional costs and potential risks, e.g. of surgical procedures. In a retrospective cohort study including 71 UC patients with concomitant PSC, the diagnosis of invisible (without visible)

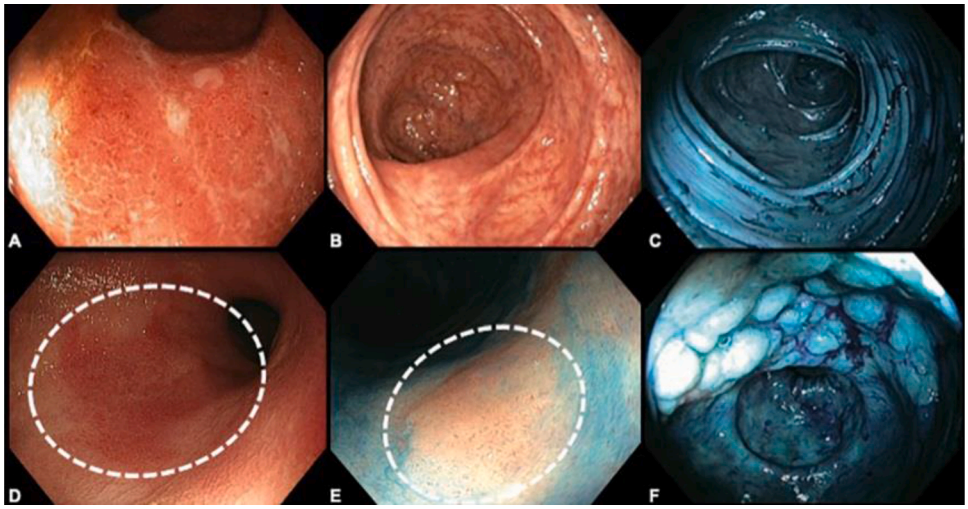

Fig. 2. Examples of endoscopy images. A: Moderate disease (the colonic mucosa shows marked erythema, absent vascular pattern, and erosions); B: Normal colonic mucosa (the colonic mucosa shows a normal vascular pattern, no erythema); C: Normal colonic mucosa (chromoendoscopy); D: Flat colitis-associated neoplasia; E: Colitis-associated neoplasia (methylene blue is rapidly absorbed by normal mucosa, but the absorption in neoplastic mucosa is impaired); F: Large colitis-associated neoplastic lesion (chromoendoscopy).

dysplasia in random biopsies, detected in eight patients, impacted clinical outcomes. [55] As high-risk patients already receive frequent surveillance, the additional impact of detecting invisible dysplasia might be overestimated, however.

Thus, to define the optimal surveillance technique when using HD endoscopes, more research is needed to determine the (cost)effectiveness of HD-endoscopy with versus without chromoendoscopy and/or random biopsies.

4.3. Unmet needs

To further improve surveillance strategies in IBD patients, we believe a novel prediction model is warranted. Such a model should be easy to implement in clinical practice, while accounting for the presence of multiple risk factors and their effect sizes. The potential place of biomarkers (e.g. aneuploidy) as prognostic factors should also be evaluated. Additionally, exit strategies for surveillance should be explored. One study indicated that after two consecutive surveillance colonoscopies without abnormalities (defined as no post-inflammatory polyps, strictures, dysplasia or CRC, or endoscopic disease activity), the subsequent risk of HGD or CRC is negligible. [56] Discontinuation of surveillance in patients at lowest risk of CRC, as is recommended in the Dutch guideline, [57] will reduce the burden for patients and the healthcare system considerably. It is presently not clear what strategy should be adopted in IBD patients in whom surveillance is discontinued. Enrolment in a nationwide, faecal occult blood test (FOBT)-based, screening program seems practical, but the accuracy of FOBT is diminished by mucosal inflammation, [58] rendering this type of surveillance less effective.

5. Management of dysplasia

Until recently, guidelines recommended to perform a proctocolectomy in case of colorectal dysplasia in patients with IBD, based on a high perceived risk of synchronous dysplasia in this setting. Nowadays, treatment of these lesions is increasingly moving towards endoscopic options, where interventions are tailored based on patient and lesion characteristics.

It must be emphasized that a diagnosis of colorectal dysplasia or cancer in IBD patients should be confirmed by a second pathologist with expertise in this field. [4, 6, 8, 46, 59] This recommendation is based on the high level of interobserver variability (especially for LGD and indefinite dysplasia) [60, 61] which, at least partly, can be attributed to the presence of histologic inflammation. [61, 62]

First, a distinction between endoscopically visible and invisible dysplasia has to be made. [46] If invisible dysplasia is detected in random biopsies, present guidelines advise to consider strict continued surveillance, reassessment by an IBD expert, or surgical treatment. [46] This choice is based on the grade of dysplasia, presence of unifocal versus multifocal invisible dysplasia, synchronous visible dysplasia as well as patient characteristics (e.g. age, comorbidity) and preferences. In case of a visible lesion, the first step is to determine whether the lesion can be resected endoscopically, and if so, which technique should be used. This depends on lesion size, shape, site (colitis-associated area or not), surface, and surrounding area (together known as Five "s" characteristics), risk of invasion (amongst others based on Five "s" criteria) and endoscopic accessibility. [46, 63] Small polypoid and non-polypoid lesions can be removed with a simple endoscopic resection technique using snares. [8] For larger lesions endoscopic mucosal resection (EMR) is used, a technique that involves lifting of the lesion from the muscularis propria using a submucosal injection with saline to permit safe removal of the lesion with a snare. Endoscopic submucosal dissection (ESD) should be considered for large (>20mm) lesions, especially if these are non-polypoid or display high-risk features. In ESD the lesion is lifted from the muscularis propria, followed by dissection of the lesion from deeper layers using an endo-knife. ESD has the advantage of high *en bloc* resection rates (even in case of submucosal fibrosis which is frequently encountered in colitis-associated lesions), high numbers of radical (R0) resections at histopathologic examination, and is associated with low risk of adverse events such as bleeding or perforation. [10] Furthermore, previous studies on ESD in IBD patients report low local recurrence rates and small numbers of metachronous lesions, although these studies have relatively short follow-up periods and small sample sizes. [10] Table 1 summarises the main advantages and disadvantages of endoscopic resections using an EMR or ESD technique. Educational videos on these techniques were previously published. [47, 64, 65] Importantly, when a lesion is successfully resected endoscopically, strict endoscopic follow-up is needed. [46]

Surgery is the treatment of choice for endoscopically non-resectable lesions, invisible dysplasia (especially in case of HGD), and/or 'high risk' colons. [46, 66] A total proctocolectomy is recommended in case of HGD or CRC, in order to also reduce the future risk of dysplasia and cancer. [8, 67] After a total proctocolectomy, a pouch (reservoir) can be constructed from the terminal ileum with an anastomosis to the anal canal, as an alternative to a permanent ileostomy. Guidelines state that in patients diagnosed with LGD not involving the rectum, or in presence of comorbidities, a subtotal colectomy with ileorectal anastomosis or ileostomy, or segment resection can be considered. [67] Importantly, after a subtotal colectomy (or even segmental colonic resection), the remaining colonic mucosa remains at risk for dysplasia and cancer. [68] Also, colectomy is associated with a 1% risk of perioperative mortality, risk of long-term complications (e.g. faecal incontinence or leakage, ileus or small bowel obstruction, fistulae) and reduced quality of life. [69, 70]

To further improve the management of dysplasia, future studies should examine the long-term oncological safety and efficacy of both advanced endoscopic resection techniques and limited surgical resections (segment resections or subtotal colectomy for endoscopically non-resectable lesions).

6. Chemoprevention

In theory, every therapeutic agent that effectively induces and maintains remission in IBD will decrease the risk of CRC, because inflammation is the main driver behind tumourigenesis in colitis-associated CRC. However, the role of maintenance therapy in the prevention of colitis-associated dysplasia and cancer is currently unclear. Most evidence for chemoprevention is based on retrospective studies with varying definitions of medication use. Moreover, most studies did not adjust for (cumulative) inflammation and should therefore be interpreted with caution.

Previous meta-analyses report a negative association of 5-aminosalicylic acid (5-ASA) use and development of dysplasia and CRC in IBD (mostly UC patients). [17, 71, 72] This finding might be explained by

Table 1
Advantages and disadvantages of EMR and ESD.

	Endoscopic mucosal resection (EMR)	Endoscopic submucosal dissection (ESD)
Resection plane	+ Submucosa	+ Submucosa
Suitable lesions	- Smaller polypoid and non-polypoid lesions	+ Large (>20mm), high-risk lesions and non-polypoid lesions
Procedure time	+ Relatively short	- Long
Learning curve	+ Relatively short	- Relatively long
Adverse events	+ Low	+/- Low, but higher than EMR
Histopathological examination	- Difficult, due to frequent piecemeal resections[1]	+ Good, due to high rate of *en bloc* resections
Radical (R0) resections rate	- Relatively low	+ High

EMR=Endoscopic mucosal resection, ESD=Endoscopic submucosal dissection.
[1]) i.e. fragmented resections, especially when treating larger lesions with EMR.

anti-inflammatory effects, direct chemoprotective properties of 5-ASA at a molecular level, or a milder phenotype of patients on 5-ASA (mono) therapy. [73] The protective effect of 5-ASA on the risk of dysplasia and CRC seems to be dose-related, which additionally supports its role in this setting. [71]

Thiopurine use has also been found to prevent the development of dysplasia and CRC. [74-76] A recent meta-analysis did not show a protective effect of TNF-alpha inhibitors on HGD and CRC. Of note, TNF-alpha inhibitors are usually prescribed in patients with more severe disease, which might have confounded the results considerably. [74] Theoretically, both thiopurines and TNF-alpha inhibitors could either decrease the risk of CRC by reducing colonic inflammation, but also increase the risk of CRC through their immunosuppressive effects.

In patients with IBD and concomitant PSC, a meta-analysis reported no overall reduction in the risk of dysplasia and CRC in patients using ursodeoxycholic acid (UDCA). However, the risk of dysplasia and CRC was lower in a subgroup of patients using low-dose UDCA (8-15 mg/kg) (OR 0.19, 95% CI 0.08-0.49). [77] In contrast, the use of high-dose UDCA (15-30 mg/kg) is reportedly associated with a trend towards an increased risk of colorectal dysplasia or cancer in pooled analysis (OR 2.03, 95% CI 0.53-7.73), [77] and other adverse outcomes such as mortality and liver transplantation. [78, 79] Current British guidelines recommend against the use of ursodeoxycholic acid for the sole purpose of preventing CRC. [80]

Overall, guidelines are not consistent with respect to prescribing specific drugs solely for chemopreventive purposes in patients not requiring maintenance therapy.

7. Conclusion

In conclusion, the risk of CRC in patients with colonic IBD is increased, especially among those with a high (prior) inflammatory burden, concomitant PSC, or a history of dysplasia. The current practice of colonoscopic surveillance aims to detect and remove precursor lesions of CRC and thereby mitigate the excess CRC risk in patients with IBD. Some studies, but not all, indicate that the CRC risk in IBD has declined over the last decades, which has been ascribed to the wide implementation of surveillance colonoscopies, advanced endoscopic techniques for mucosal visualisation and lesion resection, and improved management of inflammation.

The mainstay in the management of these patients remains colonoscopic surveillance. This resource-intensive procedure imposes a significant burden on patients, while interval CRCs still occur too frequently. In this review, we have highlighted several areas of interest for future research (Fig. 3). More research is needed to develop a prediction model to determine individualised surveillance intervals, to assess the necessity of taking random biopsies and/or using chromoendoscopy with modern HD endoscopes, and to establish the long-term efficacy and safety of advanced resection techniques such as ESD in patients with IBD.

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Authors' contributions

AW, RM: conception of the work, drafting of manuscript. BO: conception of the work. ML, BO: revising the work critically for intellectual content. All authors approved the final version of the manuscript.

Declarations of Competing Interest

None.

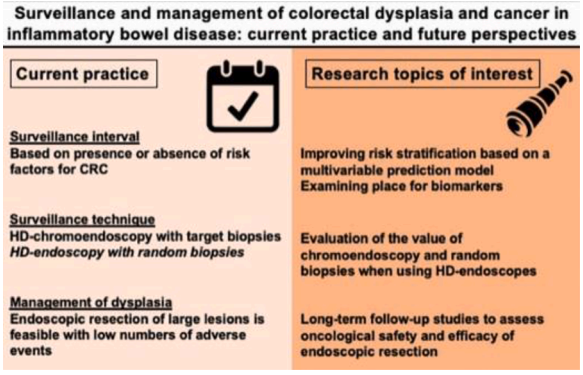

Fig. 3. Current practice and future perspectives
CRC=colorectal cancer, HD=high-definition.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2021.08.010.

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