Advanced imaging in colonoscopy: contemporary approach to dysplasia surveillance in inflammatory bowel disease

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ABSTRACT

Inflammatory bowel disease (IBD) (ulcerative colitis (UC) and Crohn's disease (CD)) is a chronic relapsing/remitting condition characterised by intestinal inflammation. One of the main concerns in patients with longstanding ulcerative and Crohn's colitis is development of colonic dysplasia and colorectal cancer (CRC), a risk higher than that of the general population. Colonoscopy surveillance programmes have been developed by major societies worldwide to improve early dysplasia detection and treatment, thus preventing progression to colorectal cancer.

Colonoscopy is an imperfect tool as lesions can be missed, an issue even more relevant to colitic patients, where mucosal inspection and lesion recognition may prove challenging. Extensive research has been undertaken on performance improvement in this area while technical advances in optical imaging, such as high-definition, have made their way into modern endoscopy units.

Techniques and technologies available to enhance optical diagnosis of dysplasia in inflammatory bowel disease are reviewed in this paper, focusing on those that are realistic, widely available and feasible for everyday practice.

INTRODUCTION

The increased risk of colorectal cancer (CRC) in ulcerative colitis (UC) and colonic Crohn's disease (CD) has led to the implementation of colonoscopic surveillance programmes. Variable CRC incidences have been reported, depending on the methodology and population studied. Population-based meta-analyses showed that the overall CRC incidence ratio in all patients with inflammatory bowel disease (IBD) is 1.7,¹ with patients with CD having a 1.9-fold² and patients with UC having a 2.4-fold³ increase in lifetime

CRC risk, compared with the general population. These rates are lower than previously thought, perhaps reflecting the positive impact of colonoscopy in detecting and managing neoplasia in early stages, or better disease management.^{4 5} Also, initial studies often involved patients from tertiary referral centres, where the risk may be higher as these patients tend to have more severe disease.⁶

The purpose of this review is to provide an outline of the techniques and technologies available to enhance optical diagnosis of dysplasia in IBD, focusing on those that are realistic and feasible for everyday practice.

INDICATIONS AND STRATEGY FOR DYSPLASIA SURVEILLANCE IN PATIENTS WITH IBD

All patients with IBD should have an 'index' colonoscopy approximately 8–10 years following their diagnosis to confirm disease extent and ascertain degree of inflammatory activity. Patients with UC with involvement proximal to the rectum and patients with CD with more than one segment of the colorectum involved should be offered surveillance. Current guidelines by the British Society of Gastroenterology (BSG) and the European Crohn's and Colitis Organization (ECCO) recommend surveillance every 1, 2–3 or 5 years for these patients, depending on the extent, activity and presence of risk factors such as postinflammatory polyps, family history of CRC, previous colonic dysplasia or stricture and concomitant primary sclerosing cholangitis (table 1).^{7–9}

Since the literature indicates that most dysplastic lesions in IBD are endoscopically

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Table 1 Risk stratification and colonoscopy intervals proposed by British Society of Gastroenterology (BSG) for dysplasia surveillance in patients with inflammatory bowel disease (IBD) (adapted by Cairns *et al*⁹)

Low risk (every 5 years)	Intermediate (every 3 years*)	High risk (annually)
<ul style="list-style-type: none"> ▶ Extensive† colitis with <i>no</i> active (endoscopic or microscopic) inflammation ▶ Left-sided‡ colitis ▶ Crohn's colitis affecting <50% of the colon 	<ul style="list-style-type: none"> ▶ Extensive colitis with <i>mild</i> inflammatory activity ▶ Postinflammatory polyps ▶ Family history of CRC in first-degree relative more than 50 years 	<ul style="list-style-type: none"> ▶ Extensive colitis with <i>moderate/severe</i> inflammation ▶ Primary sclerosing cholangitis ▶ Stricture in past 5 years ▶ Dysplasia in past 5 years declining surgery ▶ First-degree relative with CRC <50 years

*ECCO recommends surveillance every 2–3 years for intermediate-risk patients.

†UC affecting the colon proximal to the splenic flexure or CD colitis of >50% of the colon.

‡Distal to the splenic flexure.

CRC, colorectal cancer; ECCO, European Crohn's and Colitis Organization; UC, ulcerative colitis.

Table 2 Overview of current recommendations for dysplasia detection in inflammatory bowel disease (IBD) by major international societies

CRC surveillance recommendations in inflammatory bowel disease

SCENIC (2015) ¹³	<p>'When white light colonoscopy is performed, high definition is recommended rather than standard definition'</p> <p>'During standard-definition colonoscopy, chromoendoscopy is recommended rather than white-light colonoscopy'</p> <p>'When performing surveillance with high-definition colonoscopy, chromoendoscopy is suggested rather than white-light colonoscopy'</p> <p>'Narrow-band imaging is not suggested in place of standard or high definition white-light colonoscopy or chromoendoscopy'</p>
British Society of Gastroenterology (BSG) (2011) ⁷	'Pancolonic dye spraying with targeted biopsy of abnormal areas is recommended. If chromoendoscopy is not used, the strategy of random biopsy should be followed'
European Crohn's and Colitis Organization (ECCO) (2013) ⁸	<p>'Pancolonic chromoendoscopy should be performed during surveillance colonoscopy, with targeted biopsies of any visible lesion. If appropriate expertise for chromoendoscopy is not available, random biopsies (4 every 10 cm) should be performed; however, this is inferior to chromoendoscopy in the detection rate of neoplastic lesions'</p> <p>'Other image enhancement techniques such as narrow band imaging or autofluorescence have not been convincingly demonstrated to be superior to white light endoscopy or chromoendoscopy in the detection of neoplastic lesions, thus they cannot currently be recommended for colitis surveillance'</p>
European Society of Gastrointestinal Endoscopy (ESGE) (2014) ¹⁸	'Routine use of pancolonic chromoendoscopy with targeted biopsies for neoplasia surveillance in patients with long-standing colitis is recommended. In appropriately trained hands, in the situation of quiescent disease activity and adequate bowel preparation, non-targeted four-quadrant biopsies can be abandoned'

CRC, colorectal cancer.

detectable,^{10–12} substantial research has been undertaken on advanced imaging techniques that may facilitate dysplasia detection and effectively guide management.¹³

At this point, it is worth stressing that the terms 'dysplasia-associated lesion or mass (DALM)', 'adenoma/non-adenoma-like mass' and 'flat dysplasia' should be avoided, as they may lead to confusion with regard to further endoscopic management. Instead, the terms 'visible' and 'invisible' should be used to describe dysplasia within clearly identified lesions or within random biopsy samples, respectively.⁸ Visible dysplasia can further be classified as polypoid (pedunculated, sessile) and non-polypoid (superficial elevated, flat, depressed), in accordance with the Paris Classification for polyps.^{13 14}

HIGH-DEFINITION ENDOSCOPY

An endoscope's resolution defines the level of detail and sharpness of generated images. High-definition (HD) colonoscopy systems are capable of producing

an image signal of more than 1 million pixels, as opposed to standard definition (SD) ones (up to 400 000 pixels)¹⁵; hence, their ability to visualise subtle changes in the mucosal surface pattern is increased. HD colonoscopy has been extensively studied in the field of polyp detection, where a modest benefit was observed.¹⁶ Its use in IBD surveillance appears rational as dysplastic lesions in this case are frequently flat and subtle. A retrospective UK cohort study in patients with IBD undergoing surveillance concluded that HD colonoscopy leads to significantly more dysplastic lesions being diagnosed compared with SD, especially in the right colon.¹⁷ HD over SD colonoscopic surveillance is currently favoured by ECCO and the SCENIC ('Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease patients') multidisciplinary international experts' panel, given also that HD scopes are now part of most modern endoscopy suites' armamentarium (table 2).^{8 13}

Figure 1 A dysplastic lesion in a patient with long-standing pancolitis, assessed with white-light endoscopy (A) and chromoendoscopy with indigo carmine (B). Note the clearer delineation of the lesion's margins post dye spray application.

CHROMOENDOSCOPY

This technique involves the use of an absorptive or contrast dye (methylene blue 0.1% or indigo carmine 0.03%–0.5%, respectively) to enhance mucosal surface changes which are then biopsied in a targeted fashion (figure 1). The colonic mucosa is segmentally sprayed during scope withdrawal with use of a syringe and a spray catheter, directly via the endoscope's flushing channel, or with the help of a washing pump.¹⁹ Pools of residual dye are then aspirated, dyed mucosa is scrutinised and areas suspicious of dysplasia are sampled as appropriate.^{13 18 20 21} With the help of the dye, potentially dysplastic lesions may 'stand out' due to a different surface pattern from the surrounding mucosa. The Paris and Kudo classification systems may then be used to describe lesion morphology and pit pattern, respectively, as applies to sporadic polyps.^{22 23}

Several studies have looked into the yield of dysplasia of CE compared with conventional white light endoscopy (WLE).^{20 24–30} A recent meta-analysis by the SCENIC Group concluded that significantly more patients with dysplasia were identified with CE versus WLE (RR=1.8), with a per-patient incremental yield of 6%, suggesting that CE is the modality of choice when performing IBD surveillance.¹³ HD

chromoendoscopy has also been studied, with data from a back-to-back study in 75 patients showing significantly higher dysplasia yield than each modality alone (9% for HD-WLE vs 21% for HD-CE).³¹

Limitations of the CE technique have been described. As with all surveillance colonoscopies (table 3), good quality bowel preparation is essential and quiescent status of disease desirable, as inflammation may be difficult to macroscopically differentiate from potentially dysplastic areas, while it may also lead to confusing histopathology results.³² Familiarisation of the endoscopist with the technique prior to employing solely targeted biopsy approach is mandatory, even though such training has not yet been standardised.^{13 18} In addition, the impact of CE on total procedure time (mean increase by 11 min as per the SCENIC group meta-analysis¹³) raises concern in modern, busy endoscopy units. The BSG currently recommends allocating more time ('3 points') for CE than for standard '2-point' colonoscopy. It appears though that withdrawal time may eventually be shortened, parallel to the increase in number of CE procedures an endoscopist performs.³¹ In terms of safety, in vitro data point to a risk of DNA alterations when methylene blue is sensitised by white light.³³ Nevertheless, a potential oncogenic effect of methylene blue has not been proven in

Table 3 Barriers to effective inflammatory bowel disease (IBD) dysplasia surveillance

Issue	Comment
Adherence to surveillance intervals	Requires a robust recall system. Particularly relevant to patients in clinical remission, who may not be keen to have repeat colonoscopies
Quality of bowel preparation	Preparation should be good, ideally excellent
Mucosal inflammation	Active mucosal inflammation makes endoscopic detection and lesion characterisation more complex and may lead to false-positive dysplasia diagnosis in histopathology
Endoscopist expertise	Endoscopists should be familiar with both the chromoendoscopy technique and with IBD lesion characterisation. Experience is crucial for characterising detected lesions—often challenging in colitic colons. Presence of postinflammatory polyps can make identification of such abnormalities even more challenging
Equipment	HD imaging set-up and chromoendoscopy should be available for optimal surveillance
Unit capacity	Appropriate time needs to be allocated in endoscopy lists to permit chromoendoscopy and to allow for meticulous mucosal inspection during withdrawal. British Society of Gastroenterology (BSG) guidelines recommend adding 15 min per procedure

studies available so far.³⁴ Indigo carmine is not absorbed by mucosal cells; therefore, it is—in theory—safer than methylene blue.

A recent study on the cost impact of CE for IBD surveillance shows that the technique is in fact less costly than WLE with random biopsies every 10 cm.³⁵ CE may lead to fewer colonoscopies and biopsy samples when patients are risk-stratified accurately,¹⁸ which may account for this favourable effect.

DO WE STILL NEED RANDOM BIOPSIES?

Pooled analyses data show that only a small proportion (1%–1.5%) of patients with dysplasia will be missed when random biopsies are omitted during HD colonoscopy or CE.¹³ In addition, the random biopsy strategy has been criticised due to implications involving cost, clinician adherence, low dysplasia yield and minimal clinical impact.^{9 12 36} On the other hand, a large retrospective real-life cohort study from the Netherlands has recently questioned the superiority of CE over WLE with targeted and random biopsies in terms of dysplasia yield,³⁷ and authors of a randomised study from Germany found a significant yield of dysplasia in random biopsies during WLE surveillance concluding that random sampling is indispensable when CE is not performed.³⁸ Table 4 summarises data on dysplasia yield with random versus targeted biopsies in SD and HD colonoscopy compared with CE.

No firm recommendation was made in the recent SCENIC expert consensus statement on whether random biopsies should be added to targeted ones when HD colonoscopy or CE is performed, as experts did not reach agreement.¹³

DYE-LESS CHROMOENDOSCOPY

Digital chromoendoscopy (Narrow Band Imaging—NBI, Olympus) uses filters applied in the endoscope's light source to enhance mucosal vessel visibility, by narrowing blue and green bandwidths to match haemoglobin's peak absorption.³⁹ This feature can be activated on demand by pressing a button on the endoscope's handle.

In a randomised crossover study by Dekker and colleagues, NBI and SD-WLE were performed similarly in detecting dysplastic lesions in 42 patients; dysplasia was diagnosed in 19% and 17% of patients with NBI and SD-WLE, respectively.⁴⁰ A subsequent randomised crossover study of 48 patients study comparing NBI with HD-WLE showed no improvement in dysplasia yield.⁴¹ In addition, a randomised parallel-group trial

from the UK that evaluated HD-WLE versus NBI in 12 patients showed no difference in dysplasia detection (9%) in targeted biopsies between these groups.⁴² Finally, Leifeld and colleagues recently published data from a randomised trial of 159 patients showing that NBI with targeted biopsies detects similar numbers of dysplastic lesions but with less tissue samples and with a shorter procedure time than HD-WLE with random plus targeted biopsies.³⁸

A Spanish randomised crossover trial evaluated dysplasia yield of targeted biopsies during HD chromoendoscopy (HD-CE) versus NBI in 60 patients; the rate of true-positive samples was comparable in the two arms but higher NBI lesion miss rates led to the conclusion that the modality cannot be recommended as a standard surveillance technique.⁴³ Three subsequent studies also failed to show a significant advantage of NBI over CE^{44–46} in dysplasia detection. Of note, NBI procedures were shorter than CE ones by 11 to 12 min.¹³

In summary, data so far do not support a clear benefit of digital chromoendoscopy (NBI) over conventional WLE or chromoendoscopy and is not currently recommended as an alternative of HD colonoscopy and CE (table 2). In addition, the cost of NBI capable colonoscopes versus the relatively cheap contrast agents and spraying kits, obviously raises an issue.⁴⁷

Two other major manufacturers (Fujinon and Pentax) have developed technologies to enhance surface pattern contrast, based on real-time virtual reprocessing of captured footage via spectrum analysis software (FICE and I-SCAN, respectively).³⁹ No data exist to date on performance of these modalities in CRC surveillance for patients with IBD.

OTHER ADVANCED IMAGING MODALITIES

Autofluorescence imaging (AFI) is performed using a specially designed endoscope fitted with a separate charge-coupled device (CCD) that takes advantage of the difference in endogenous fluorophores between normal colonic and neoplastic tissue.^{48 49} Data so far point to AFI being a highly sensitive technique in identifying dysplastic lesions. In a randomised tandem study from the Netherlands, the WLE dysplasia miss rate was 50% whereas AFI detected all lesions.⁵⁰ Despite promising data, several caveats such as the cost of AFI equipped endoscopes, difficulty in image interpretation and high false-positive rates due to artefacts (mainly because of stool residue) have not allowed AFI to be established as a mainstream modality.^{48–50}

Table 4 Dysplasia yield of targeted versus random biopsies in various surveillance techniques, based on pooled analyses data reported in the SCENIC consensus statement

	SD colonoscopy	HD colonoscopy	Chromoendoscopy
Percentage of patients with dysplasia on targeted biopsies	80.4% (95%–94%)	90.6% (80.1%–95.9%)	90.2% (85%–94%)
Percentage of patients with dysplasia on random biopsies	19.6% (11.5%–31.2%)	9.4% (4.1%–19.9%)	9.8% (6%–15%)

Confocal laser endomicroscopy (CLE) allows for 'real-time histology' of lesions that have already been detected during colonoscopy, via intravenous administration of stains such as fluorescein. Laser light can then be focused with the use of special probes or scope attachments to make subcellular imaging possible.^{48 49} This technique appears useful in scrutinising lesions already detected by WLE or CE colonoscopy, but is obviously not as practical as a total-colon surveillance method. Despite encouraging data^{26 30} showing high dysplasia detection and good lesion characterisation properties, the steep learning curve and the cost (up to US\$175 000 for a probe-based system) of this time demanding technique has so far limited its application outside clinical research settings.^{13 48 49 51}

Similar to CLE, *endocytoscopy* (EC) is a novel technique that allows highly magnified (up to 1400×) images of subcellular structures (nucleus, cytoplasm) to be obtained.⁵² Probe-based systems or EC-fitted endoscopes are used to obtain histology-equivalent images of the mucosa, following pretreatment with mucolytic agents and staining with dyes such as methylene blue and crystal violet.⁵³ So far, a pilot study has demonstrated that EC may accurately differentiate inflammatory cell populations in IBD, with prognostic implications, but no studies on dysplasia surveillance have been published to date.⁵⁴ Data on the ability of EC to detect high-grade intraepithelial neoplasia in polyps, as well as to identify early dysplastic changes as part of the adenoma carcinoma sequence, shows promise for future applications in colitis-associated dysplasia.^{55 56}

Molecular imaging involves the application of fluorescent substances (antibodies, nanoparticles, lectines, peptides) that act as probes, targeting specific molecular targets that play a role in gastrointestinal disease pathogenesis.^{57 58} Fluorescent signal can then be detected and quantified with CLE. Preclinical data from murine and human series have showed promising results. Mitsunaga and colleagues used an enzymatically activatable probe to detect cancer on a background of colitis in a murine model; cancerous and dysplastic cells displayed a much higher signal than inflamed tissue, a finding that was confirmed by histology.⁵⁹ A recent phase 1 study by Atreya and colleagues revealed that patients with Crohn's disease with increased expression of membrane-bound tumour necrosis factor (mTNF), as detected following application of a fluorescent antibody to mTNF (probe), showed higher response rates to anti-TNF treatment than patients with low mTNF expression. This has obvious potential in stratifying patients before deciding on anti-TNF therapy.⁶⁰ Molecular imaging is a rapidly evolving field which may have a significant impact on individualised patient management in the future.⁶¹

Finally, it remains to be seen whether novel approaches such as *stool DNA testing* for genetic

alterations that are part of the carcinogenesis cascade in IBD (eg, BMP3 and mNDRG4) can facilitate management of these patients and lead to improved colonoscopy yield and, consequently, better patient outcomes.⁶² Assays based on cytobiology of exfoliated colorectal cells have performed promisingly well in detecting cancerous and precancerous lesions.⁶³ Similarly, molecular tissue testing for alterations in mucosal antigens, cellular DNA content (eg, mutations in p53 and APC genes) and aneuploidy is an appealing approach, although the predictive value of these changes is unclear.⁶

MANAGEMENT OF IBD-ASSOCIATED DYSPLASIA

As most colonic dysplastic lesions in patients with IBD are considered endoscopically visible,^{10–12} current guidelines advocate endoscopic excision of visible (flat or polypoid) dysplastic lesions when possible, regardless of dysplasia grade. If biopsies from the surrounding mucosa and rest of the colon are dysplasia free, one may offer close colonoscopic surveillance rather than colectomy, provided complete excision has been achieved. The finding of multifocal or invisible dysplasia calls for a thorough discussion with the patient regarding risks and benefits of adopting a conservative approach (continued strict colonoscopy surveillance, ideally with HD equipment plus chromoendoscopy, by an experienced endoscopist) or colectomy.^{7–9 13 64} A proposed algorithm for management of dysplasia in patients with IBD is shown in [figure 2](#).

CONCLUSION

The introduction of advanced imaging techniques, mainly HD colonoscopy and CE, has increased the rates of dysplasia diagnosis in patients with IBD, with invisible (ie, found on random biopsies) dysplasia accounting for only 10% of all cases.¹³ As all colitis surveillance patients are by definition a high-risk population,⁷ it seems appropriate that wherever possible, their surveillance should be performed by experienced endoscopists using chromoendoscopy with HD equipment.

Currently, the BSG, ECCO and the American Society of Gastrointestinal Endoscopy (ASGE) recommend chromoendoscopy with targeted biopsies of visible lesions as the preferred surveillance method, where equipment and expertise are available, and preparation and degree of inflammation permits. Random, traditionally four samples every 10 cm, plus targeted biopsies should be obtained when chromoendoscopy is not available. It is noteworthy that when SD-WLE is performed, up to 20% of dysplasia is discovered in samples taken randomly.^{7 8 13 14 18} [Figure 3](#) presents a proposed algorithm on endoscopic modalities and biopsy protocols of choice in various settings.

It has to be noted that the true impact of increasingly higher dysplasia recognition with advanced endoscopy on overall CRC mortality has not been clarified.^{65 66}

Figure 2 Proposed algorithm for the management of dysplasia in patients with inflammatory bowel disease (IBD).

*Dysplasia grade to be confirmed by second experienced pathologist, considering high inter-observer variability. Series show up to 9-fold increase in CRC risk in patients with LGD. [†]Decisions should follow detailed discussion with patient and take into account age and comorbidities.

Figure 3 Proposed algorithm on endoscopic modalities and biopsy protocols of choice in various settings.

*All efforts should be made for the patient to be in remission during surveillance, to prevent difficulties in endoscopic identification of potentially dysplastic lesions and prevent histopathology confusion. [†]CE, chromoendoscopy; HD, high-definition; SD, standard definition. [§]At least 4 samples every 10 cm.

Data from a recent published study analysing 40 years of IBD surveillance at St Mark's Hospital (London, UK) show that high definition and chromoendoscopy have led to an increase in dysplasia rates from 3.7% to 5%, reaching 8.6% when HD and CE are combined. Cancers tended to be diagnosed at an earlier stage and incidence ratios of interval cancers (ie, those diagnosed between two scheduled screening procedures) also declined.⁴ However, there was no decrease in all-stages CRC rates over time in the St Mark's series,⁴ while

recent data on surveillance from three Dutch referral centres disputed the advantage of targeted CE biopsies over the random sampling approach.³⁷ As data on the aggressiveness of early dysplastic lesions are also equivocal,⁸ one may argue that patients are subjected to frequent unnecessary procedures, due to overdiagnosis.

Further prospective data are needed to define the true, real-life, long-term impact of increased dysplasia detection via chromoendoscopy and HD colonoscopy to IBD-related CRC survival. The cost-effectiveness of

these modalities as well as issues involving proper endoscopists' training to establish minimum performance standards and eliminate interobserver variability in lesion recognition are still areas of debate.

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