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Advanced Endoscopic Imaging for Surveillance for Dysplasia and Colorectal Cancer in inflammatory Bowel Disease: Could the Pathologist be Further Helped?

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ABSTRACT

Patients with inflammatory bowel disease (IBD) have an increased risk of developing intestinal cancer. The magnitude of that increased risk as well as how best to mitigate it remain a topic of ongoing investigation in the field. It is important to quantify the risk of colorectal cancer in association with IBD. The reported risk varies widely between studies. This is partly due to the different methodologies used in the studies. Because of the limitations of surveillance strategies based on the detection of dysplasia, advanced endoscopic imaging and techniques involving the detection of alterations in mucosal antigens and genetic abnormalities are being investigated. Development of new biomarkers, predicting future occurrence of colonic neoplasia may lead to more biomarker-based surveillance. There are promising results that may lead to more efficient surveillance in IBD patients and more general acceptance of its use. A multidisciplinary approach, involving in particular endoscopists and pathologists, together with a centralized patient management, could help to optimize treatments and follow-up measures, both of which could help to reduce the IBD-associated cancer risk.

Patients with inflammatory bowel disease (IBD) have an increased risk of developing intestinal cancer. The magnitude of that increased risk as well as how best to mitigate it remain a topic of ongoing investigation in the field. Although only 1% of all cases of colorectal cancer (CRC) occur in patients with ulcerative colitis (UC) or Crohn's disease (CD), patients with IBD represent one of the highest risk groups for developing this dreaded complication.[1,2] A meta-analysis of 116 studies found the mean age of UC-CRC diagnosis to be 43.2 years.[3] Lakatos and coworkers[4] found the average age of IBD-CRC diagnosis to be 10-15 years younger than sporadic CRC in Eastern Europe (50.9 years vs. 62.2 years). The prognosis for sporadic CRC and IBD-CRC is similar, with a 5-year survival of approximately 50%.[5] Identifying at-risk patients and implementing appropriate surveillance for these patients is central to managing the CRC risk in IBD.[6]

It is important to quantify the risk of CRC in association with IBD. The reported risk varies widely between studies. This is partly due to the different methodologies used in the studies.

The aim of this review is to examine the magnitude of the risk of CRC in IBD patients, quantifying the risk factors, and especially to focus on the importance of surveillance for CRC in IBD patients, paying attention to the new techniques to detect early dysplasia and cancer.

MAGNITUDE OF RISK

Data about the magnitude of the risk of CRC in IBD patients come from tertiary referral centers, district general hospitals, and population-based studies. Information from tertiary centers is likely to regard patients with severe disease who are probably at greater risk of IBD-CRC.

The early studies included patients who had already been referred with a diagnosis of CRC and those admitted to hospital with IBD, rather than gold-standard population-based studies, which have a lower proportion of patients with severe or extensive colitis, which are *per se* adverse prognostic factors for increased risk of CRC. The increased risk of CRC in UC has long been established.

As mentioned above, a meta-analysis of 116 studies, performed by Eaden and coworkers, including overall 54,478 UC patients, with 1698 cases of IBD-CRC, found an overall prevalence of CRC in UC of 3.7%, increasing to 5.4% in those with pancolitis. The analysis included studies from a wide variety of centers and from different geographical areas. Interestingly, the studies from the United Kingdom and the United States found a higher incidence [4 and 5 per 1000 person-years duration (pyd), respectively] than those from Scandinavia (2 per 1000 pyd).[3]

A population-based cohort study performed by Ekbom and coworkers on 3117 patients with UC, who were diagnosed between 1922 and 1983, gave a standardized incidence ratio of 5.7 [95% confidence interval (CI), 4.6-7.0] as compared with the expected incidence of CRC in the general population.[7] In another population-based study performed by Soderlund and coworkers on 7607 patients with IBD who were diagnosed between 1954 and 1989, the standardized incidence ratio was 2.3 (95% CI, 2.0-2.6) as compared with the general population.[8] Other recent population-based studies have suggested a much lower risk of IBD-CRC.

In the study performed by Jess and coworkers on 378 patients from Olmsted County with UC for a total of 5567 pyd (1940-2004), the annual crude incidence was found to be 0.10% and the cumulative risk of CRC at 30 years proved to be as low as 2%. The authors concluded that the risk of CRC is only increased in patients with extensive colitis.[9]

Bernstein and coworkers obtained data about 2672 patients with UC between 1984 and 1997, and they found an annual risk of 0.16% for colon cancer and 0.06% for rectal cancer.[10]

The prospective study by Rutter and coworkers, performed on 600 patients with extensive UC for 5932 pyd as part of a colonoscopic surveillance program (1970-2001), found a cumulative probability of IBD-CRC of 7.6% and a decreasing incidence over the period studied.[11]

A Hungarian population-based study that followed 723 UC patients (1974-2004) calculated the cumulative risks according to disease duration: 0.6% after 10 years, 5.4% after 20 years, and 7.5% after 30 years, whereas Winther and coworkers[12] followed 1160 patients with UC (1962-1987) and gave an annual crude incidence of 0.06% and a cumulative risk of 2.1% at 30 years. However, this study is from Denmark, where the colectomy rate is one of the highest in the world, a fact that may affect the results and underestimate the risk of IBD-CRC, whereas Hungary has a high rate of sporadic CRC and a low rate of colectomy for non-CRC reasons; these factors may result in a higher rate of CRC.

More recently, another study performed by Jess and coworkers on CRC risk in a nationwide cohort of 47,374 Danish patients with IBD over a 30-year period, showed a low rate of CRC. For patients with UC, the overall relative risk (RR) for CRC decreased from 1.34 (95% CI, 1.13-1.58) in 1979-1988 to 0.57 (95% CI, 0.41-0.80) in 1999-2008. Among patients with CD, the overall RR for CRC was 0.85 (95% CI, 0.67-1.07), which did not change over time. According to the authors, the decreasing risk for CRC from 1979 to 2008 might have resulted from improved therapies for patients with IBD.[13]

Interestingly, other studies have shown that Crohn's colitis carries a similar magnitude of risk for the same disease extent. A Canadian cohort study matched a population-based IBD database to a cancer registry in North America between 1984 and 1997, although a limitation of this study was the lack of definition of disease site or extent. There were 2857 cases of CD and 2672 of UC. There was an increased incidence of CRC for patients with Crohn's [risk ratio (RR), 2.64; 95% CI, 1.69-4.12] or UC (RR, 2.75; 95% CI, 1.91-3.97) as compared to the general population but no statistically significant difference between the two IBDs.[14] The authors of the study found the risk of rectal cancer to be increased in UC (RR, 1.90; 95% CI, 1.05-3.43) but not in Crohn's colitis (RR, 1.08; 95% CI, 0.43-2.70).

Ekbom and coworkers also studied the risk of CRC in CD. In their cohort study of 1655 patients performed in Sweden,

patients with terminal ileal CD had the same risk of CRC as the general population but those with colonic CD had an RR of 5.6 (95% CI, 2.1-12.2).[15]

RISK FACTORS

Ulcerative colitis
Several factors have been identified that increase the risk of CRC in patients with UC, related to the disease and to the host. Among the former, the duration of disease is an important risk factor, as shown by the fact that the cumulative risk of cancer increases over time, as mentioned above.[3,7] Second, considering CRC risk as being associated with the cumulative effect of chronic inflammation, the extent of colon involvement in UC is an independent predictor of cancer risk.[7] In this connection, the study performed by Ekbom and coworkers showed that the RR of CRC was 1.7 for ulcerative proctitis, whereas the risk in left-sided colitis was 2.8 and this risk rose to 14.8 in patients with extensive colitis.[7] Third, considering the degree of mucosal inflammation, Rutter and coworkers demonstrated in their retrospective series that severity of inflammation on biopsy independently predicted risk of CRC.[16] This finding was supported by two other studies in which inflammatory activity was shown to be independently associated with CRC risk.[17,18] Additionally, it was also shown that backwash ileitis may be an independent predictor of increased CRC risk.[19]

With regard to the risk factors related to the host, a younger age at diagnosis is also associated with an elevated risk of CRC, independent of disease duration.[7] This may be because patients with an early age of diagnosis tend to have more severe inflammation.[16] Considering gender, Söderlund and coworkers[8] observed that the relative risk in males was 2.6 (95% CI, 2.2-3.1) and in females 1.9 (95% CI, 1.5-2.4) compared with the general population, whereas the cumulative incidence at 40 years after diagnosis of IBD was 8.3% in males and 3.5% in females. Similar results were found in a Swedish study performed by Ekbom and coworkers.[7]

Furthermore, a family history of CRC, independent of a family history of IBD, is associated with a higher risk of developing this neoplasia.[20-23] Finally, considering the comorbidity of UC patients, a meta-analysis by Soetikno and coworkers on the risk of CRC in UC patients with coexistent primary sclerosing cholangitis (PSC), described an odds ratio of 4.09 (95% CI, 2.89-5.76) when compared to UC patients without PSC.[24] This result has led to the recommendation of closer surveillance in this unique at-risk subset of UC patients. Furthermore, the location of colon cancer seen in PSC patients (right side predominant) should be carefully considered as this finding may help to influence the surveillance approach.

In conclusion, consistent data support the oncogenetic impact of chronic inflammation (and IBD, in particular) in colorectal mucosa. Thus the "adenoma–carcinoma" sequence of sporadic cancers becomes the "inflammation–dysplasia-carcinoma" sequence in IBD. On a clinical level, the link between inflammation and IBD-related neoplasia relies on the well-known correlation between cancer risk and disease activity, extent, and duration.[25]

Among the risk factors examined in this literature review, the severity of inflammation appears to be the only modifiable risk factor, thus underscoring the importance of chemoprevention in mitigating cancer risk, and therefore the need for a preventive approach to the early detection of CRC.

The most recent meta-analysis of population-based studies associated UC with a 2.4-fold risk of CRC, which represents an overall 1.6% CRC rate (including sporadic cases) during the first 14 years of follow-up for UC patients.[26] Indeed, the declining trend in the incidence of CRC among UC patients gives the impression that combining the control of UC-related inflammation with surveillance strategies is highly effective in CRC secondary preventions and suggests that appropriate levels of vigilance should be maintained in high-risk patient populations.[25]

Crohn's disease
The evaluation of the risk of CRC in CD poses several methodological challenges, related to the heterogeneous nature of the disease, with many patients having no colonic involvement, and considering that even among patients with Crohn's colitis it is difficult to assess the extent of colonic inflammation, given that the disease can involve any area of the colon in a patchy distribution, and that many Crohn's patients have undergone partial surgical resection of the colon, removing some of the at-risk tissue. This could justify the wide variation among the studies estimating the risk of CRC in CD.

Gyde and coworkers reported a relative risk (RR) of CRC in Crohn's colitis of 23.8, whereas the risk was 4.3 in the general CD population,[27] whereas Greenstein and coworkers calculated an RR of 6.9 for developing CRC in isolated colonic CD.[28] Another study showed an RR of CRC of 5.6 for those only with colonic involvement, as compared to an RR of 3.2 for patients with ileocolitis and 1.0 for patients with ileal involvement only.[29] These studies indicate that CD implies a higher risk of CRC, but also that this risk correlates with the extent of colonic involvement.

A meta-analysis of 12 hospital-based and population-based studies on CRC risk in CD revealed an overall RR of CRC in all the patients of 2.5 (95% CI, 1.3-4.7),[30] whereas in the subset of patients with colonic disease this risk rose to 4.5 (95% CI, 1.3-14.9), and for patients with ileal

disease only the risk was not significantly different from the general population. The cumulative risk of CRC for all patients with CD, regardless of disease distribution, was 2.9% after 10 years, 5.6% after 20 years, and 8.3% after 30 years of disease. This finding is in contrast to the Jess meta-analysis, which included population studies of intestinal cancer risk in CD,[31] where the estimation of RR of CRC ranged from 0.9 to 2.2, with a pooled estimate of 1.9 (95% CI, 1.4-2.5).

Gillen and coworkers compared the risk of CRC in patients with extensive Crohn's colitis and in patients with extensive UC,[32] showing a cumulative risk of CRC of 8% at 22 years for patients with CD versus 7% at 22 years for patients with UC. With regard to the risk factors for CRC in CD, CD patients share many of the same risk factors for CRC as UC patients (ie, younger age at diagnosis, greater extent of colonic involvement, and longer duration of disease). Furthermore, bypassed segments of bowel[33] and perianal fistulae[34] in CD may also be sites at increased risk for carcinogenesis, just as bowel strictures may harbor dysplasia or cancer[35] and should be carefully biopsied and resected if a pediatric or upper endoscope cannot traverse them.

Actually it is really difficult to establish exactly the risk of CRC in CD, although it is generally accepted that patients with CD of the colon are at increased risk for dysplasia and CRC, and that this risk is related to the cumulative effect of colonic inflammation, as in UC. With the exception of strictures as mentioned above, screening and surveillance of CRC in patients with CD should be handled identically to patients with UC, matched for extent of colonic involvement.

In summary, the more recent studies mentioned above, which follow a more representative proportion of all patients with IBD,[13] demonstrates that the risk of CRC is lower than previously thought. Furthermore, the influence of time of disease seems to be much less significant and more important factors such as inflammatory burden and disease extent should guide the surveillance approach. Table 1 shows the confirmed risk factors and proposed protective factors for developing CRC in IBD patients and Table 2 shows the characteristics of the studies evaluating the risk factors for CRC in IBD patients.

SURVEILLANCE: THE PAST

Ideally, only a randomized controlled trial, with a very large number of patients and a long follow-up, could assess whether surveillance reduces CRC-related mortality. To date, only case-control studies have provided information about this topic. A Cochrane review[36] performed by Collins and coworkers revealed only three case-control studies, in the current literature, that addressed the question of whether

Table 1: The confirmed risk factors and proposed protective factors for developing CRC in IBD patients

Confirmed risk factors	Proposed protective factors
Extent of colitis	5-ASA treatment
UC pancolitis	
UC left-sided colitis	
CD colitis	
Disease duration	UDCA treatment
Association with PSC	Folate supplementation
Family history of CRC	Maintainance of remission
Age at diagnosis	Mucosal healing
Active inflammation	
Pseudopolyps	
Strictures	
Degree of inflammation	
Bypassed segments of bowel	

CRC: Colorectal cancer, IBD: Inflammatory bowel disease, OR: Odds ratio, LGD: Low-grade dysplasia, PSC: Primary sclerosing cholangitis, CI: Confidence interval, HR: Hazard ratio, ASA: Acetylsalicylic acid, UDCA: Ursodeoxycholic acid

surveillance programs reduce CRC-related mortality.[37-39] In the first one, Lashner and coworkers[37] found an improved overall survival but not a reduced mortality from CRC [RR, 2.09; 95% CI, 0.39-11.12]. In the second one, Karlen and coworkers[38] reported a protective effect, although not statistically significant, of surveillance colonoscopy on CRC-related mortality. In fact two of the 40 patients who died from CRC had undergone at least one surveillance colonoscopy compared with 18 of the 102 controls (RR, 0.29; 95% CI, 0.06-1.31). Only one patient who died from CRC had had at least two surveillance colonoscopies (RR, 0.22; 95% CI, 0.03-1.74), thus indicating a possible "dose"–response relationship. Finally, Choi and coworkers[39] showed that CRC in IBD patients undergoing surveillance is detected at an earlier stage (P = 0.039). The authors of the abovementioned meta-analysis concluded that there was indirect evidence for improved survival from colonoscopic surveillance.

The goal of colorectal cancer screening colonoscopy in the general population and surveillance in IBD patients is to detect premalignant changes early enough that intervention can prevent complications of invasive cancer. Dysplasia, assessed by histology, remains the most reliable marker of cancer-prone IBD patients.[25] Its detection depends on the timing of the endoscopic follow-up, on the endoscopic techniques employed during the follow-up, on the quality and the quantity of the biopsy samples obtained, on the endoscopist's and pathologist's expertise, and on the patient's compliance with the recommended follow-up.[1,25] The mandatory operation in IBD-associated dysplasia is colectomy, because of the high prevalence of synchronous or metachronous cancer, as well as the technical limitations of being able to identify confidently and completely resect dysplastic lesions in flat mucosa.[40]

Table 2: Summary of the characteristics of the studies evaluating the risk factors for CRC in IBD patients

Study (Author, year)	Study design	Prognostic factors for recurrence or progression of dysplasia or cancer	Frequency of surveillance	Population
Eaden *et al.* (2001)	Meta-analysis of 116 studies	Duration of disease Extent of disease	-	24,478 people with ulcerative colitis 1698 with CRC
Jess *et al.* (2005)	Meta-analysis of 6 studies	Gender Extent of disease	-	6538 people with Crohn's disease 55 with CRC
Soetikno *et al.* (2002)	Meta-analysis of 11 studies	PSC	-	16,844 people with ulcerative colitis 564 with ulcerative colitis and PSC 560 with CRC, including 60 with ulcerative colitis and PSC
Thomas *et al.* (2007)	Meta-analysis of 20 studies	Displasia at diagnosis	-	Over 2677 people with ulcerative colitis 508 with LGD 31 with CRC
Askling *et al.* (2001)	Retrospective (assumed) cohort, with nested case– control	Extent of disease Family history	-	19,876 people with ulcerative colitis or Crohn's disease 143 with CRC
Brentnall *et al.* (1996)	Prospective cohort	Age at diagnosis Duration of disease PSC	-	45 people with ulcerative colitis 20 with PSC 13 with dysplasia
Broome *et al.* (1992)	Retrospective (assumed) cohort	Age at diagnosis Duration of disease PSC	-	72 people with ulcerative colitis 5 with PSC 17 with dysplasia, carcinoma, and/or DNA aneuploidy
Broome *et al.* (1995)	Retrospective (assumed) cohort	PSC	-	120 people with ulcerative colitis 40 with PSC and ulcerative colitis 7 with CRC
D'Haens *et al.* (1993)	Retrospective case– control	Age at diagnosis PSC	-	58 people with ulcerative colitis 29 with PSC 9 with CRC
Ekbom *et al.* (1990)	Retrospective (assumed) cohort	Gender Age at diagnosis Duration of disease Extent of disease	-	1655 people with Crohn's disease 12 with CRC
Florin *et al.* (2004)	Retrospective case– control	PSC	-	384 people with ulcerative colitis 90 with PSC 8 with CRC
Friedman *et al.* (2001)	Retrospective (assumed) cohort	Age	-	259 people with Crohn's disease 5 with CRC
Gilat *et al.* (1988)	Prospective (assumed) cohort	Duration of disease	-	1035 people with ulcerative colitis Number with CRC not reported
Gupta *et al.* (2007)	Retrospective cohort	Gender Age at diagnosis Duration of disease Extent of disease PSC Severity of inflammation	HR 1.7 (95% CI 0.9 to 3.0) for association of frequency of colonoscopy (1 or more per year) with any neoplasia HR 3.9 (95% CI 1.3 to 11.4) for advanced neoplasia (univariate only)	418 people with ulcerative colitis 65 with any neoplasia 15 progressed to advanced neoplasia
Gyde *et al.* (1988)	Retrospective cohort	Gender Age at diagnosis Duration of disease Extent of disease	-	823 people with ulcerative colitis 38 with CRC
Hendriksen *et al.* (1985)	Retrospective (assumed) cohort	Duration of disease Extent of disease	-	783 people with ulcerative colitis 7 with colonic cancer
Jess *et al.* (2006)	Retrospective (assumed) cohort	Age at diagnosis Type of IBD Extent of disease PSC Location of dysplasia	-	692 people with IBD 29 with colorectal dysplasia

Table 2: Contd...				
Study (Author, year)	Study design	Prognostic factors for recurrence or progression of dysplasia or cancer	Frequency of surveillance	Population
Jess *et al.* (2007)	Retrospective (assumed) cohort, with nested case– control	PSC Family history Severity of inflammation	Adjusted OR 5.3 (95% CI 1.4 to 20) for colorectal neoplasia if one or more colonoscopic surveillances during the disease course compared with no surveillance	145 people with IBD 43 with neoplasia
Karlén *et al.* (1998)	Retrospective cohort, with nested case– control	-	RR 0.29 (95% CI 0.06 to 1.31) for risk of CRC mortality if colonoscopic surveillance ever compared with never. RR 0.43 (95% CI 0.05 to 3.76) for risk of CRC mortality if one colonoscopic surveillance compared with never. RR 0.22 (95% CI 0.03 to 1.74) for risk of CRC mortality if two or more colonoscopic surveillances compared with never	142 people with ulcerative colitis 40 with CRC (deaths)

CRC: Colorectal cancer, IBD: Inflammatory bowel disease, LGD: Low-grade dysplasia, PSC: Primary sclerosing cholangitis, OR: Odds ratio, CI: Confidence interval, HR: Hazard ratio

In the general population, the dysplastic or premalignant lesion is the colon polyp that can be easily visualized and resected at the time of the colonoscopy before it transforms into a malignant lesion. In contrast, dysplasia in IBD can be found at sites distant from the cancer itself or before the cancer develops and is difficult to recognize on colonoscopy, as it often arises from flat, normal-appearing mucosa.[41]

IBD-related dysplasia usually presents with marked macroscopic variability. In fact it can be found, similar to flat dysplasia, in random biopsy specimens obtained from unremarkable mucosa; on the other hand, it can occur within or near plaque-like lesions or raised polypoid masses, defined as dysplasia-associated lesion or mass (DALM).

More recently, the definitions of adenoma-like mass or dysplasia (ALM or ALD) have been proposed. ALM is applied to polypoid dysplasia with no adjacent flat component, endoscopically indistinguishable from a sporadic (sessile or pedunculated) polyp and completely removable by endoscopy; in this case, histology is of little help in differentiating DALM from ALM and this distinction basically relies on endoscopy.[25]

Because IBD-CRC is preceded by dysplasia, finding dysplasia on random colon biopsies represents an increased risk of developing colorectal cancer in the near future. Dysplasia is classified as indefinite, low-grade, and high-grade.

IBD-CRC occurs in areas of chronic inflammation and can be a polypoid, ulcerated, or plaque-like lesion. Most IBD-CRCs are adenocarcinomas, but there is a higher incidence of poorly differentiated, anaplastic, and mucinous carcinomas compared with sporadic colorectal cancer.[40]

The best technique for surveillance is evolving. Currently, endoscopists are moving away from using random colonic biopsies toward targeted biopsies aimed at abnormal areas identified by newer colonoscopic techniques (chromoendoscopy, confocal microendoscopy, narrow band imaging). In this connection, although dysplasia has been shown to be highly predictive for cancer in many studies, the time-consuming process of multiple random biopsies and sometimes inconclusive pathology findings still form the basis for doubt among many gastroenterologists.

Furthermore, many studies have shown a low number of biopsies taken during surveillance, suggesting that this strategy is challenging to comply with.

The risk of IBD-CRC is estimated based on duration and extent of disease, coexistent risk factors (PSC, family history of sporadic CRC), and endoscopic and histological findings at colonoscopy. The surveillance intervals are based on this risk assessment.[42]

International guidelines recommend systematic surveillance in patients with a history of 8-10 years of extensive UC,

or 15 years of left-sided UC, whereas earlier surveillance is not recommended. Surveillance colonoscopies should be performed when the disease is in remission. The guidelines also recommend obtaining 2-4 random colon biopsy specimens every 10 cm with additional samples of any suspicious areas.[43-48] Table 3 shows the characteristics of the main studies on surveillance for CRC in IBD patients. Table 4 shows the main differences between the recommendations, arising from the international guidelines, for colorectal cancer surveillance programs in IBD patients.

ROLE OF THE PATHOLOGIST IN THE DETECTION OF DYSPLASIA AND COLORECTAL CANCER IN INFLAMMATORY BOWEL DISEASE

The detection of dysplasia and colorectal cancer in IBD depends, as mentioned above, on several variables: (1) the frequency of colonoscopy and the technique used; (2) the quality and quantity of the biopsy samples obtained; (3) the endoscopist's and pathologist's expertise; and (4) the patient's compliance with the recommended follow-up.[1,25]

Histology in expert hands remain the most reliable way to identify cancer-prone cases (dysplasia patients). In fact, after delivery of paraffin-embedded biopsy samples to the pathologist, the pathologist is concerned with the microscopic examination of the biopsy samples, the determination and classification of dysplasia, and the confirmation of the suspicions of the endoscopist. The histological assessment of biopsy specimens (from wherever they were obtained) is fundamental to patient's management: It is ultimately the pathologist's interpretation that distinguishes high-risk from low-risk patients and triggers recommendations to continue surveillance or opt for colectomy.[25]

However, the detection and the characterization of dysplasia has several well-recognized limitations, including its low intra- and inter-observer variability (even among experts).[49,50]

In both prospective and retrospective studies, inter-observer consistency in the histological assessment of dysplasia has ranged between 42% and 72%.[51-57] Furthermore, Lim and coworkers[57] found a kappa coefficient between 10 pairings of five gastrointestinal pathologists in the range of 0.6 (acceptable) to 0.39 (unacceptable). Such agreement is naturally best when the two extremes of the histological spectrum of the lesions are considered (no dysplasia versus high-grade dysplasia), while the diagnostic consistency is worse when distinguishing between the intermediate categories.[41,58] Due to this lack of concordance, the international guidelines strongly recommended that dysplasia, as assessed prior of any surgical treatment, must be confirmed by a second, experienced gastrointestinal pathologist.[48,59,60]

SURVEILLANCE: THE PRESENT AND THE FUTURE

There have been recent advancements in optical methods and dye systems to more accurately detect dysplasia.

These techniques may allow for targeted biopsies and eliminate the need for random biopsies. The most promising technique to date and one that has been endorsed recently by the Crohn's and Colitis Foundation of America Colon Cancer in IBD Study Group[48] is chromoendoscopy. In this technique, a dye such as methylene blue or indigo carmine is applied to the colon either randomly or selectively to highlight areas of dysplasia. Methylene blue is an absorptive dye that is taken up by normal tissue but not dysplastic tissue, and indigo carmine is a contrast dye that pools in areas of abnormal dysplastic tissue.

The pioneering studies performed by Kiesslich *et al.*[61] and Rutter *et al.*[62] have shown increased dysplasia detection with chromoendoscopy compared with conventional colonoscopy. Indeed, Rutter and coworkers[62] did not find any dysplasia in 2904 random biopsies utilizing conventional colonoscopy, while nine dysplastic lesions were detected in 157 targeted biopsies with indigo carmine chromoendoscopy, seven of which were only visible with dye spraying.

Table 3: Characteristics of the main studies on surveillance for CRC in IBD patients		
Author (year)	**Choi *et al.* (1993)**	**Lashner *et al.* (1990)**	**Karlen *et al.* (1998)**
Population	People with ulcerative colitis of at least 8 years duration and extension of disease proximal to the sigmoid colon (*n*=50)	People with extensive ulcerative colitis (defined as continued disease from any point proximal to the splenic flexure to the distal rectum) of at least 9 years' duration (*n*=186)	People with extensive and longstanding ulcerative colitis (*n*=142)
Intervention	Surveillance with biopsies every 2 years (every 3 years in the early years of the programme) after negative results on two consecutive annual examinations	People had 4.2±3.0 (range 1–16) colonoscopies during the study period at a mean of 17.0 years after symptom onset	Two of 40 patients with UC and 18 of 102 controls had undergone at least one surveillance colonoscopy. Twelve controls but only one patient with UC had undergone two or more surveillance colonoscopies
Comparator	No surveillance	No surveillance	No surveillance

CRC: Colorectal cancer, IBD: Inflammatory bowel disease, UC: Ulcerative colitis

Table 4: Summary of the main differences between the recommendations arising from the international guidelines for colorectal cancer surveillance programmes in inflammatory bowel disease patients

Guidelines	Beginning of surveillance	Surveillance schedule	Biopsy protocol	New endoscopic technique recommended
U.K. 2002	8-10 yr (pancolitis) 15-20 yr (left-sided colitis)	3 yr (2nd decade) 2 yr (3rd decade) 1 yr (4th decade)	33+	Not mentioned
AGA 2010	8 yr (pancolitis) 15 yr (left-sided colitis)	Every 1-2 yr	33+	Not mentioned
ACG 2010	8-10 yr	Every 1–2 yr	33+	Not yet
ECCO 2008	8 yr (pancolitis) 15 yr (left-sided colitis)	2 yr (1st–2nd decade) −1 yr (3rd decade)	33+ If no chromoendoscopy	Chromoendoscopy
BSG 2010	10 yr	−3 yr lower risk −2 yr intermediate risk −1 yr higher risk	33+ If no chromoendoscopy	Chromoendoscopy
German Guidelines 2010	8 yr (pancolitis) 15 yr (left-sided colitis)	Annually	33+	Not yet

U.K.: United Kingdom, AGA: American gastroenterology association, ACG: American college of gastroenterology, ECCO: European crohn's and colitis organization, BSG: British society of gastroenterology

Successively, several studies have shown that chromoendoscopy increases sensitivity for the detection of dysplasia. A recently published meta-analysis calculated a pooled incremental yield of chromoendoscopy over white light for dysplasia detection. The authors were able to find that in six studies on 1277 patients, chromoendoscopy was significantly better than white light for the detection of dysplasia in colonic IBD.[63]

In the technical review and position statement published by the AGA, the authors concluded that targeted biopsies using chromoendoscopy performed by endoscopists experienced in this technique is a reasonable screening alternative to the random sampling of colon using standard white light.[64,65]

In the AGA Institute technology assessment of image-enhanced endoscopy (IEE), the authors concluded that IEE may increase the yield of detection of dysplasia and as such is recommended for patients with long-standing UC.[66]

Finally, The British Society of Gastroenterology (BSG) advises that all patients with IBD should have a screening colonoscopy approximately 10 years after symptom onset (ideally when the patient is in remission) with pancolonic dye spraying and targeted biopsies of abnormal areas.[42]

The surface guidelines for the application of chromoendoscopy in IBD patients with longstanding colitis and mucosal healing were developed to provide a better standardization of this technique.[67]

However, the use of surface dyes during chromoendoscopy in some cases has generated safety concerns. Prior *in vitro* biochemical studies have established that in the presence of light, methylene blue can generate single-strand breaks in DNA. As an alternative to methylene blue, indigo carmine is generally regarded as a safe dye because it is not absorbed by the colonic mucosa. To date, however, no long-term data exist that capture adverse clinical outcomes, and some groups continue to use methylene blue chromoendoscopy.[68]

Furthermore, chromoendoscopy presents multiple other potential limitations; the mucosa is not always equally sprayed, areas of colorant pooling prevent proper visualization, and, most importantly, it tends to be more time-consuming. It is also virtually impossible to perform chromoendoscopy in the context of poor colonic cleansing and in the presence of severe colonic inflammation where a neoplasia-like pit pattern is often seen, potentially producing false-positive results.[69]

With regard to the costs of the procedure the accessories needed to perform tissue staining are readily available and relatively inexpensive (208 US dollars for the Olympus Reusable kit, 67 US dollars for the Wilson-Cook Medical single-use kit, and 225 US dollars for the Hobbs medical single-use kit). However, there is no specific Current Procedural Terminology (CPT) code for billing and reimbursement for the time and effort added to the endoscopic procedure.

Other techniques that are currently under study but are not yet proved for widespread clinical use include confocal microendoscopy and narrow-band imaging.

Confocal laser endomicroscopy (CLE) allows imaging of the mucosal layer, including epithelial cells and the lamina propria. The targets of endomicroscopic examination for an accurate diagnosis can be the cells, vascular structures, and/or tissue patterns.[70] In addition, if an immediate diagnosis cannot be

obtained by CLE, the same technique offers the possibility of targeted biopsies. The pathologist will receive fewer biopsy specimens but will find more specific tissue because a greater number of "intelligent" biopsy specimens containing target tissue are provided by the endoscopist.[71]

Confocal endomicroscopy has been proposed as an addition to chromoscopically detected lesions to help target biopsies and reduce their number. In a study by Kiesslich and coworkers, chromoendoscopy reduced biopsies 10-fold. The addition of confocal could have reduced the number of biopsies a further fivefold to approximately one per patient. Although there is the possibility of having to perform very few biopsies, the technique is technically demanding and the instruments currently unwieldy.[72]

CLE is possible after injecting 2.5-5 mL fluorescein 10% intravenously. A confocal miniaturized laser with a defined wavelength of 488 nm generates *in vivo* histology images up to a 1000-fold magnification. During ongoing endoscopy, single cellular and subcellular tissue analyses 0-250 μm in depth are visible. In patients with UC, targeted biopsies of mucosal areas suspected of harboring intra-epithelial neoplasia can be identified directly while performing the colonoscopy.

The main limitation of CLE is that this technique is only limited to a very small mucosal surface; furthermore, the high costs of CLE (90,000 US dollars for the whole system) should be evaluated in a further cost-effectiveness analysis.

An alternative technique to CLE is the miniprobe-based endomicroscopy technique. After the miniprobe is passed through a 2.8-mm working channel of any standard videoendoscope, the laser unit generates a confocal image with a high frame rate per second. Special attention toward this technique has taken place since a high-resolution miniprobe device was developed.[72]

With regard to narrow band imaging (NBI), there was great hope that NBI would be able to act as a form of "electronic chromoendoscopy" to make colitis surveillance more efficient. Unfortunately, probably due to background inflammation, dysplasia detection was no different to white light in two tandem studies and one multi-center, randomized, parallel group study.[73-75] Furthermore, recently a prospective, randomized crossover study was published to compare NBI and chromoendoscopy for the detection of intraepithelial neoplasia: NBI appears to be a less time-consuming and equally effective alternative to CE for the detection of intraepithelial neoplasia. However, given the NBI lesion and patient miss rates, the authors did not recommend it as the standard technique.[76] Similarly, a meta-analysis to determine whether use of NBI enhances the detection of adenomas, compared with conventional colonoscopy, was recently performed; there was no statistically significant difference in the overall adenoma detection rate with the use of NBI or WLC [36% vs. 34%; $P = 0.413$ (RR, 1.06; 95% CI, 0.97-1.16)], and there was no statistically significant difference in polyp detection rate by using NBI or WLC [37% vs. 35%; $P = 0.289$ (RR, 1.22; 95% CI, 0.85-1.76)).[77] For these reasons, it seems unlikely that NBI will be helpful for dysplasia detection in colitis.

The cost of NBI is 70,500 US dollars for the whole system (including endoscope, processor, and light source).

Endocytoscopy is a kind of reflecting light microscopy and the device is passed through a 3.7-mm working channel of any suitable endoscope. The magnification ranges from 450- to 1100-fold depending on the device and the *in vivo* recognition of surface cells is possible after topically applying acylcysteine for mucolysis and methylene blue for staining. So far, there are no published data on this technique in patients with IBD.[78]

Some innovative endoscopy imaging techniques are under current evaluation to prove their eligibility for clinical routine endoscopy. Optical coherence tomography is an optical analogue to endoscopic ultrasound with an imaging depth of 2 mm. The device is also used in a "mother–baby fashion" through the working channel of the endoscope as mentioned above. There are two publications on this technique in patients with IBD.[79,80]

These studies have started to show the feasibility of this method and to differentiate transmural inflammation in CD from patterns of active UC.

Fluorescence endoscopy is a technique to assess intra-epithelial neoplasia after topical or systemical sensitization with 5-aminolevulinic acid (5-ALA). After the application of 5-ALA, this substance is converted intracellularly into the fluophore protoporphyrin IX, which accumulates selectively in neoplastic tissue making it possible to detect a reddish spot while illuminated with blue monochromatic light (442 nm). The first report that evaluated fluorescence endoscopy in patients with UC was published in 2003.[81] This study examined 37 patients with UC and found a sensitivity of 87%-100% after local application and 43% after systemic application with 5-ALA. The specificity was lower with 62% after systemic and 51% after local sensitization. However, 3 years later another study could not confirm these results and evaluated 682 biopsies in 42 patients with IBD. The corresponding histology in two patients with intraepithelial neoplasia showed no correlation with the red fluorescent areas during fluorescence endoscopy.[82] However, neither optical coherence tomography nor fluorescence endoscopy is currently suitable for the detection of intraepithelial neoplasia in patients with IBD.

Finally, *in vivo* histology techniques are the basis for further diagnostic improvement on a single cellular level and have opened the door for molecular imaging in the gastrointestinal tract. There is one *in vivo* mouse model where colonic tissue samples are incubated with fluorescein-marked antibodies against epithelial growth factor receptor; in this mouse model a confocal microscope was able to detect the epithelial growth factor receptor on the surface of tissue after inducing colitis.[83] The first *in vivo* detection of dysplastic crypts by confocal microscopy in humans during ongoing endoscopy was possible after topical application of fluorescent-labeled heptapeptides, which were identified previously to bind to premalignant tissue as high-affinity ligands.[84]

FUTURE PERSPECTIVES

Because of the limitations of surveillance strategies based on the detection of dysplasia, further techniques involving the detection of alterations in mucosal antigens and genetic abnormalities are being investigated.[85,86] For example, it was shown that sialosyl-Tn is a mucin-associated carbohydrate antigen that may presage the development of dysplasia and CRC by several years.[87,88] Similarly, allelic deletions and point mutations of tumor suppressor genes, such as p53, Rb, mcc, and APC (adenomatous polyposis coli) have been found in dysplastic and cancerous UC.[85,87,89]

It is likely that changes in nuclear DNA content are detectable earlier than histological signs of premalignancy. As a result, detection of DNA aneuploidy by flow cytometry of mucosal specimens in UC patients may be more objective and less sensitive to assessment error than dysplasia.[86] DNA aneuploidy detected by these techniques has been correlated with dysplasia and carcinoma.[90-92] However, as with dysplasia, the predictive value of aneuploidy is uncertain. Neoplasms can arise without preexisting aneuploidy, and conversely, aneuploidy may exist for many years without progression to malignancy.

Furthermore, stool-based molecular tests hold a large potential for improving colorectal cancer screening. Recent advances in the development of molecular markers in fecal specimens are encouraging for its use as a screening tool. Genetic mutations and epigenetic alterations that result from the carcinogenetic process can be detected by coprocytobiology in the colonocytes exfoliated from the lesion into the fecal matter. These markers have shown promising sensitivity and specificity in the detection of both malignant and premalignant lesions and are gaining popularity as a noninvasive technique that is representative of the entire colon.[93]

CONCLUSIONS

IBD shows an increased risk for developing CRC; in this setting, surveillance colonoscopy detects early neoplastic lesions and reduces colitis-associated mortality.

However, endoscopists are moving away from using random colonic biopsies toward targeted biopsies aimed at abnormal areas identified by advanced endoscopic imaging, when high-quality bowel cleansing and inactive mucosal disease are guaranteed.

Development of new biomarkers predicting future occurrence of colonic neoplasia may lead to a more biomarker-based surveillance. These are promising results that may lead to more efficient surveillance in IBD patients and more general acceptance of its employment.

Furthermore, the clinico-pathological link between IBD and CRC is well defined and provides the rationale for a differentiated endoscopic surveillance of patients with IBD without dysplasia, lesions indefinite for dysplasia or low-grade dysplasia, considering that patients with "late-onset" IBD should be considered "more prone" to cancer development. A multidisciplinary approach, together with a centralized patient management, could help to optimize treatments and follow-up measures, both of which could help to reduce the IBD-associated cancer risk (25). Therefore, physicians should apply into routine clinical practice:
- The simplification of dialogue between endoscopist and pathologist, to optimize patients' management, together with
- The application of educational measures to improve patients' awareness, thus optimizing the acceptance to both treatments and follow-up strategies.

ACKNOWLEDGMENTS

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