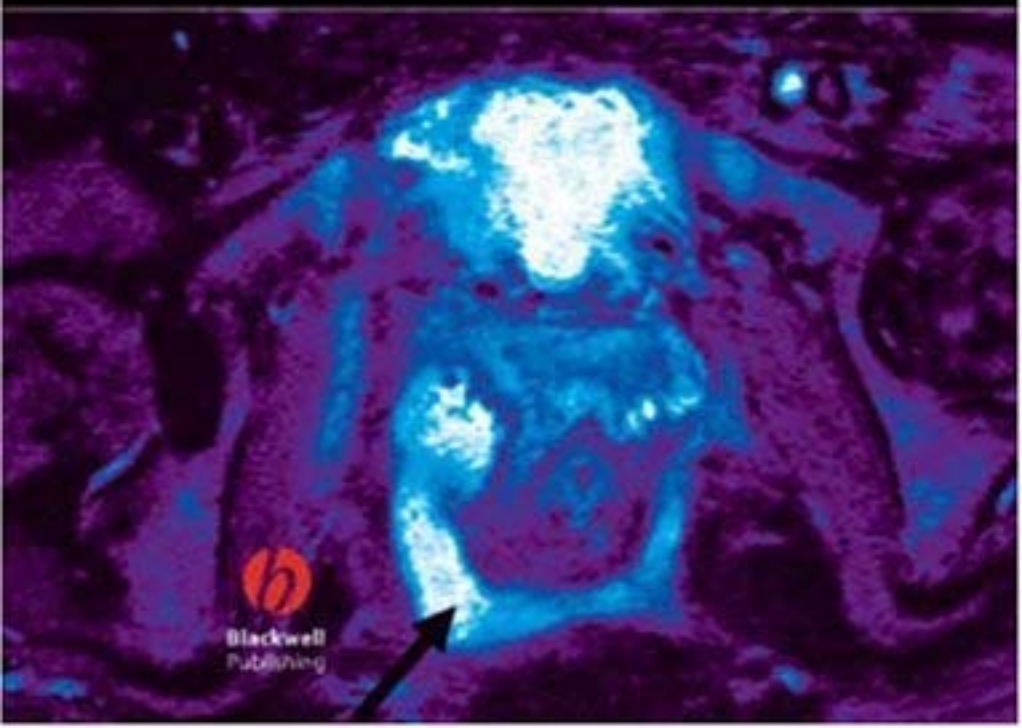
Clinical Dilemmas in Inflammatory Bowel Disease

Edited by Peter Irving, David Rampton and Fergus Shanahan



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Preface

In early 2004, we instigated at Barts and The London a weekly lunchtime clinical and academic IBD meeting. This is a multidisciplinary meeting, open not only to adult medical consultants and trainee gastroenterologists, but also to others including colorectal surgeons, pediatric gastroenterologists, nurses, the nutrition team, specialist pharmacists, visitors to the Unit, laboratory researchers and medical students: the average attendance is about twenty. During the meetings, we discuss patients we have encountered during the previous week who have presented difficult management problems, as well as practical day-to-day administrative issues. In addition, we decided at the outset of these meetings to ask, in rotation, attending staff each to give a 15-minute presentation on a discrete, current, controversial, important, practical, and often as yet unresolved topic relating to the care of patients with IBD. The subjects are selected by discussion between the group, and one talk is presented each week. The talks have proved extremely popular, both for the audience and the presenter, and it is out of them that the idea for this book arose.

Accordingly, this book contains a series of pithy, we hope enjoyable, sometimes provocative, but generally evidence-based articles on IBD topics which have been selected with a view to covering many of the areas that cause clinicians difficulties in decision making. As we have deliberately chosen some controversial topics, we should perhaps point out that as editors we do not necessarily agree with all that is written here; if we did the book might prove dull. In line with its origins, some of the chapters of the book have been written in the first instance by younger gastroenterologists, prior to final touches being added by established experts.

We hope that this approach will appeal both to consultant and trainee gastroenterologists, as well as other members of the IBD team. Inevitably, the book will soon become out of date, but we hope that in the interim readers will find that it provides a useful distillation and analysis of a wide range of current management dilemmas. Indeed, we hope that you might read the odd chapter on the bus or in the train, if not in the lavatory or on the beach.

We are very grateful to all our co-authors, almost all of whom delivered their chapters on time and with minimal hassling. We are particularly grateful too to the team at Blackwell's: Alison Brown for her enthusiasm about the project when we first discussed it with her, Fiona Pattison, Mirjana Misina and Linda Bolton for all their editorial work.

PMI, DSR, FS
March 2006

Clinical Dilemmas in Inflammatory Bowel Disease
Edited by Peter Irving, David Rampton, Fergus Shanahan

Part 1 Investigating IBD in the 21st Century

1 Capsule endoscopy: do we need it?

JOEL E D MAWDSLEY & MARK APPLEYARD

LEARNING POINTS

Capsule endoscopy

- Capsule endoscopy (CE) has a diagnostic yield of 40–70% in patients with suspected small bowel Crohn's disease where other investigations have been normal
- It is not yet clear whether CE provides additional information about the small bowel in patients with known Crohn's disease
- There is an emerging role for CE in differentiating Crohn's disease from indeterminate colitis
- Small bowel follow through (SBFT) is not reliable in predicting capsule retention and the role of the patency capsule is evolving
- SBFT before CE may in due course prove unnecessary in suspected small bowel Crohn's disease

Introduction

In addition to being the section of the gastrointestinal (GI) tract most commonly affected by Crohn's disease, the small bowel (SB) is also the most difficult region to visualize endoscopically. Wireless video capsule endoscopy (CE) is a new technology which, at least in part, overcomes this problem, by allowing complete non-invasive endoscopic imaging of the small bowel.

However, for CE to have a role in the diagnosis and management of small bowel Crohn's disease, it should fulfill several criteria: it should be safe, provide additional diagnostic information and its use should lead to clinically meaningful changes in patient management. In this chapter we discuss the limitations of other small bowel imaging techniques, the potential uses of CE in relation to Crohn's disease and the evidence to support its use in each scenario.

Limitations of other techniques for imaging small bowel

Imaging of the SB has been previously limited to the radiologic techniques of small bowel follow through (SBFT), enteroclysis (double contrast small bowel examination) and computed tomography (CT) enteroclysis, and the endoscopic techniques of push enteroscopy, double balloon enteroscopy and colonoscopy with ileal intubation.

SBFT is the most common technique used to assess small bowel Crohn's but it is relatively insensitive for subtle mucosal lesions. Enteroclysis and CT enteroclysis are more invasive than SBFT, requiring the passage of a catheter into the duodenum under sedation, and several investigators have found these techniques to be no more sensitive [1]. All three techniques result in significant radiation exposure, limiting the frequency with which they should be performed.

Push enteroscopy can only view the proximal small bowel 15–160 cm beyond the ligament of Treitz and is more invasive and technically difficult than CE. Double balloon enteroscopy is an exciting new technology which has the potential to biopsy and perform therapeutic endoscopy throughout the small bowel. However, the examination is invasive, time consuming and may not examine the entire small bowel even when the procedures are performed per orally and per anally. Visualization of the terminal ileum at colonoscopy is limited both to the distal 10–15 cm of SB and to those patients in whom the terminal ileum can be successfully intubated.

TABLE 1.1 Trials assessing the role of capsule endoscopy in the diagnosis and assessment of Crohn's disease.

Reference	N	Preceding investigation	Yield (%)	Comparator	Yield (%)
Diagnosis of small bowel Crohn's					
Fireman [5]	17	SBFT, EGD, colonoscopy (ileoscopy 6/17)	71	N/A	N/A
Ge [6]	20	SBFT, EGD, colonoscopy	65	N/A	N/A
Herrerias [7]	21	SBFT, EGD, colonoscopy (ileoscopy 17/21)	43	N/A	N/A
Arguelles-Arias [8]	12	SBFT, EGD, colonoscopy	75	N/A	N/A
Liangpunsakul [9]	40	SBFT, EGD, colonoscopy	7.5	CT enteroclysis	0
Eliakim [10]	35	N/A	73	SBFT CT enteroclysis	23 20
Voderholzer [11]	5	SBFT, EGD, colonoscopy	40	CT enteroclysis	40
Assessing disease activity/recurrence					
Buchman [12]	30	N/A	70	SBFT	67
Voderholzer [11]	8	N/A	75	CT enteroclysis	75
De Palma [15]	8	SBFT, OGD, colonoscopy, push enteroscopy	75	N/A	
Debinski [14]	10	N/A	N/A	CDAI, IBDQ, CRP	N/A
Differentiating SB Crohn's from indeterminate colitis					
Mow [13]	22	N/A	59	Ileoscopy	23
Whitaker [16]	7	Colonoscopy and ileoscopy	29	N/A	

CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; CT, computed tomography; IBDQ, Inflammatory Bowel Disease Questionnaire; N/A, not available; EGD, esophagogastroduodenoscopy; SBFT, small bowel follow through.

Capsule endoscopy

The Pillcam® capsule endoscope from Given Imaging© was first used in clinical trials in 2000 and was granted Food and Drug Administration (FDA) approval in 2001 (Table 1.1). Since then it has been used in over 200 000 individuals.

Capsule endoscopy images are different from standard endoscopic images. The images are seen through intestinal content without air insufflation. Minimum standard terminology is being developed to allow consistent image description, but more validation with histology is required [2]. In a recent large randomized placebo-controlled trial looking at intestinal inflammation in patients on non-steroidal anti-inflammatory drugs, 7% of those on placebo had small bowel abnormalities [3]; these data raises the question of what constitutes a normal small bowel appearance.

The appearance of Crohn's disease at CE ranges from gross mucosal ulceration and stricturing to subtle mucosal breaks and denuded villi. A CE scoring index has been proposed along the lines of the endoscopic ones, but has not been fully validated [4].

Diagnosis of suspected small bowel Crohn's disease

The majority of trials examining the role of CE in the management of Crohn's disease have studied the diagnostic yield of CE in patients with symptoms and features suggestive of Crohn's who have undergone normal SBFT, esophagogastroduodenoscopy (EGD) and colonoscopy (with attempted ileal intubation in some).

In prospective analyses of this nature, CE appears to provide significant additional information, with a diagnostic

yield ranging between 43% and 71% [5–8]. Furthermore, in all of these studies the positive findings at CE led to a change in management with a resulting improvement in most patients (83–100%), although treatment outcomes are not well reported.

In a retrospective analysis, the diagnostic yield was lower at 7.5% [9]. However, CE compared favorably to enteroclysis and CT enteroclysis, which were reported as normal in all the patients with positive findings at CE. In addition, all the patients responded to instigation of medical therapy.

Other studies have compared the sensitivities of CE with other techniques for diagnosing SB Crohn's disease, by performing the tests in a sequential, blinded manner. In a study comparing sequential SBFT, CT enteroclysis and CE, Eliakim *et al.* [10] found the sensitivities for Crohn's to be 23%, 20%, and 73%, respectively. Volderholzer *et al.* [11] found CE made a new diagnosis of SB Crohn's in two of five patients with unexplained diarrhea, both of whom had normal prior CT enteroclysis.

In summary, current evidence suggests that CE has a diagnostic yield of 40–70% in patients with symptoms suggestive of Crohn's disease where SBFT, OGD and colonoscopy with attempted ileal intubation have been normal. Direct comparison of diagnostic yield with enteroclysis and CT enteroclysis favors CE. The new diagnosis of Crohn's by CE has led to the institution of a beneficial new treatment regimen in most patients.

Assessment of disease activity and recurrence

Few trials have examined whether CE is useful in assessing the SB in patients with known Crohn's. Buchman *et al.* [12] found SBFT and CE to have similar diagnostic yields at 66% and 70% in patients with suspected disease recurrence while Voderholzer *et al.* [11] found CE and CT enteroclysis each to have a diagnostic yield of 75%. Mow *et al.* [13] suggested three or more ulcers were diagnostic of Crohn's; they found CE was diagnostic in 40% and suspicious for Crohn's in 30% of patients, but did not make additional diagnoses compared with ileoscopy.

In a study to assess its potential for detection of early postoperative recurrence of Crohn's, the diagnostic yield of CE was 75% in patients with previous SB resection and suspected recurrence who had had normal SBFT, OGD, colonoscopy, and push enteroscopy [14].

Only one study has examined the role of CE in assessing response to therapy. In this, improvements in mucosal appearance at CE were seen in 8/10 patients given infliximab [15]; these correlated with changes in Crohn's Disease Activity Index (CDAI), Inflammatory Bowel Disease Questionnaire (IBDQ) scores and C-reactive protein (CRP).

In summary, CE appears to detect recurrent small bowel Crohn's disease with a diagnostic yield of approximately 70%. However, it is not clear whether CE adds usefully to the information provided by conventional imaging techniques in this setting, nor do we yet know whether findings at CE lead to beneficial changes in management. It is therefore too early to define the role for CE in the assessment of response to therapy and of postoperative disease recurrence.

Differentiating Crohn's disease from indeterminate colitis

In a retrospective study, CE detected SB lesions suspicious of Crohn's in 13/22 patients with a previous diagnosis of indeterminate colitis and in five led to a change in management [13]. There was, however, no comparison made to other conventional imaging techniques or to the use of antibodies to *Saccharomyces cerevisiae*/antineutrophil cytoplasmic antibody (ASCA/ANCA) serology. In a second study, CE identified lesions characteristic of CD in 2/7 patients with a diagnosis of indeterminate colitis and ongoing pain and/or diarrhea, all of whom had already undergone non-diagnostic ileoscopy [16].

Is capsule endoscopy safe in Crohn's disease?

In all of the studies discussed above, SBFT was performed prior to CE and patients with significant stricturing were excluded from CE. CE retention occurred in 1/71 (1.4%) patients with suspected Crohn's, and in 4/80 (5%) patients with known Crohn's disease. In the trials of suspected SB Crohn's, very few patients were excluded because of abnormal radiology and radiology did not reliably prevent retention; SBFT may not therefore be required prior to CE in this setting.

Concerns regarding capsule endoscope retention have lead to the development of the Patency capsule. This has the same dimensions as the Pillcam® capsule but contains only a simple tracer and is designed to disintegrate in the GI tract 40–100 hours after ingestion. In a multicenter study, the Patency capsule was passed intact in 41/80 patients with

known small bowel strictures of whom 33 then underwent conventional CE. There were no cases of capsule retention although some patients did report abdominal pain [17].

Tolerability and capsule failure

In all the studies discussed, with the exception of patients in whom it was retained, the capsule was easily swallowed and well tolerated. Although there are no comparative preference data in these studies, in a different analysis 49/50 patients preferred CE to push enteroscopy [18].

In those studies where the data were given, the capsule failed to reach the colon before the end of its 8 hour battery life in 25/132 cases (failure rate 19%). However, in most cases, an incomplete examination did not affect diagnostic efficacy.

Conclusions

Although the number of studies is small, current evidence suggests that there is a role for CE in the diagnosis of suspected SB Crohn's disease. However, more work is required to determine the clinical significance of the more subtle mucosal lesions and whether CE can safely be performed without prior radiology. A role for CE in assessing patients with indeterminate colitis is slowly emerging but its role in assessing disease recurrence is less clear. The Patency capsule is likely to prove useful in patients with known or suspected small bowel strictures.

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Clinical Dilemmas in Inflammatory Bowel Disease
Edited by Peter Irving, David Rampton, Fergus Shanahan

Part 1 Investigating IBD in the 21st Century

2 Pathology reports – pitfalls for the unwary*

WILFRED WEINSTEIN

LEARNING POINTS

Pathology reports

- Communication between pathologist and endoscopist is crucial and must be two-way
  - Do not force the pathologist to make unrealistic diagnoses or rush to judgment
  - Encourage the pathologist to avoid using hackneyed, vague, misleading, or non-actionable diagnoses
  - The endoscopist's ego strength should be sufficient to allow the pathologist to complain about poor quality biopsies, lack of clinical information, or unrealistic expectations
  - Educate each other! Send references of clinicopathologic importance in IBD to the pathologist
- Ask questions that reflect *what is possible* to determine from biopsy pathology
- Include clinical information relevant to the differential diagnosis

Introduction

Pitfalls in pathology reports are a product of misunderstanding or miscommunication in regards to the role of biopsy in the differential diagnosis of UC and Crohn's disease. Colonic biopsy has a limited role *by itself* in the initial evaluation, differential diagnosis, and subsequent management of inflammatory bowel disorders. However, when taken together with the history, endoscopic findings, and clinical course it may significantly help to make the case for one type of IBD rather than another [1,2].

Pitfalls occur with the too-oft practice of not providing the pathologist with an adequate history and endoscopic description, or with unrealistic expectations of what biopsy can do in management. The pathologist may not have sufficient information about the clinical manifestations and therapy of the disorders. This results in failure to be descriptive alone, when the endoscopist pressures naively or prematurely for a single diagnosis. Compounding the pitfalls is the "silence of the pathologists" who put up with no historical or endoscopic information, inadequate biopsies, and unrealistic expectations. They rarely communicate these deficiencies to the clinician [3].

Special problems and how to minimize the risk of errors

Ulcerative proctitis

A biopsy is taken within a 10-cm segment of apparent diffuse inflammation in the rectum and the endoscopist asks the pathologist to "rule out ulcerative proctitis." The pathologist should never make this diagnosis unless a biopsy taken approximately 10 cm upstream is normal; that

*UNWARY: adj: not alert to danger or deception; "seduce the unwary reader into easy acquiescence" *[The American Heritage® Dictionary of the English Language,* 4th edn, Copyright © 2000 by Houghton Mifflin Company]. Not alert: easily fooled or surprised. Heedless, gullible [from dictionary.com].

rules out proctosigmoiditis. If the proximal biopsy is normal then one can have the "ulcerative proctitis talk" with the patient, indicating that 90% of the time the disorder does not migrate proximally [4]. If the endoscopist does not consider other possible relevant causes of ulcerative proctitis when biopsies are taken, an erroneous report is inevitable; as in mucosal prolapse due to solitary rectal ulcer syndrome (SRUS), mucosal trauma from digital removal of stool, anal intercourse, sexually transmitted disease [5], and ischemic proctitis, especially after aortoiliac bypass surgery.

Questions for the pathologist and avoiding unrealistic expectations

(Table 2.1)

"Rule out Crohn's disease"

This guarantees that the pathologic diagnosis will be *compatible with Crohn's disease* because almost any histologic findings are compatible with Crohn's disease. The solution is for the clinician to ask the pathologist if there are findings of focal inflammation in diffusely abnormal mucosa endoscopically and if there are non-crypt cell granulomas (because granulomas next to partially degraded crypts are a feature of UC). Neither finding clinches the diagnosis of Crohn's but the question alerts the pathologist that you are looking for more solid evidence than any small collection of inflammatory cells.

TABLE 2.1 Lesion descriptions, relevant medications, history, and questions for the pathologist. (After Weinstein [3])

Lesion description
Simple language for mucosal abnormalities: thick folds rather than hypertrophic; define friability if used, i.e. single pass petechiae or bleeding; or spontaneous petechiae or oozing
Describe what was seen rather than an interpretive term such as colitis
Key drugs
Type of preparation (enemas or oral)
Current IBD treatment
Any other immunosuppressives (e.g. after transplantation)
Chemotherapy or radiotherapy (and when last treatment with same)
Current or recent NSAIDs, cocaine, methamphetamine
Current or recent antibiotics
History
Brief usually suffices
Duration of diarrhea, bloody or non-bloody
Risk factors for other disorders (see section on ulcerative proctitis)
Underlying cardiac or vascular disease if present
Question for the pathologist
Be as specific as possible (see text)

NSAIDs, non-steroidal anti-inflammatory drugs.

"Rule out UC in a patient with diffusely abnormal mucosa"

My favorite question in apparent UC endoscopically is in two parts:

1 *"It looks like UC but are there features to suggest something else?"* This alerts the pathologist to look for disorders that can mimic UC, such as infectious colitis (acute self-limited) or multifocal non-crypt associated granulomas that would suggest Crohn's disease or ischemic bowel. In endoscopically classic UC, biopsies help most when the findings do not fit.

2 *"Are there classic signs of underlying UC?"* This refers to crypt branching and subcryptal inflammatory infiltrates.

"Is it UC or Crohn's disease?"

Settings where that distinction is difficult to impossible in a single series of biopsies at any point in time include [2]: fulminant colitis, treated IBD, mild IBD, and new onset UC in children. A meeting of the two solitudes (clinician and pathologist) will: (i) inform the clinician about these special situations; and (ii) empower the pathologist to avoid being a collaborator in providing a definitive diagnosis when that is not possible. Fulminant or highly severe UC can be transmural and resemble Crohn's disease. In treated UC, mild UC, and in childhood UC at presentation (even with moderate to severe symptoms), the rectum may be spared and the inflammation more severe in proximal than distal parts of the colon [2,6]. Thus, Crohn's might be the erroneous diagnosis based upon patchiness and rectal sparing. Overall, the best time to make the distinction between UC and Crohn's disease in adults is in the untreated state when there are active but not fulminant symptoms.

The rush to judgment

The endoscopist should not rush to judgment, and furthermore not press the pathologist to collaborate in a rush to judgment. In patients with shorter term histories of diarrhea it may be most prudent to simply call it colitis, leave open the possibility of a self-limited disease, and treat with the usual drugs. The most common error we make is the knee

jerk label of Crohn's for any focal endoscopic involvement. Drug-induced colitis (non-steroidal anti-inflammatory drugs [NSAIDs], cocaine, methamphetamines) might be responsible for a Crohn-like or an ischemic picture [7]. Aphthous lesions from PhosphoSoda preparations occur commonly in the left colon. Ischemic colitis appearances on biopsy may be produced by infections, not just the classic *Escherichia coli* OH:157, but also others such as *Salmonella*, *Shigella*, *Clostridium difficile*, and *Campylobacter jejuni*.

Biopsies taken near diverticula to look for IBD

But the endoscopist does not tell the pathologist about the diverticulosis. A bona fide segmental colitis, only in an area of diverticula, may represent diverticular colitis and not some other focal disease such as Crohn's disease [8] (see Chapter 61).

Colitis in the immunocompromised patient

In patients with common variable immunodeficiency, undergoing chemotherapy or radiotherapy, or with human immunodeficiency virus (HIV) with low CD4 counts, and after transplantation, the main role of the endoscopist is to rule out infectious causes or endogenous changes such as chemotherapy or radiation change. UC or Crohn's disease are difficult if not impossible diagnoses to make with assurance in these settings.

The pathologist's vague, meaningless, or non-actionable terminology1

Mild chronic inflammation is the greatest pandemic affecting the gastrointestinal tract. Usually these are cases with normal mucosa. Mild inflammation is present in the right colon in health, accompanied by scattered eosinophils and crypt mucus depletion, but not cryptitis. If the pathologist is not aware of this regional difference or if the endoscopist mixes right and left sided colonic biopsies into one fixative bottle, then irrelevant diagnoses may result for the unwary clinician.

Non-actionable terms unfortunately still abound. **Moderate dysplasia** in the colon is not a standard dysplasia grade, and there is no published action plan for it. **Unqualified atypia** may lead to panic and the term should not be used unless accompanied by the adjective of **regenerative-type** atypia.

Clinical correlation recommended. What does this mean? Many pathologists use this as a covert term for "I'm concerned" or "I don't know what's going on histologically" to fit the clinical and/or endoscopic picture. Either sentiment is permissible. The solution is to remove the phrase and phone the clinician, or transmit any special concern in the pathology report.

Indeterminate colitis. This term should not be used in biopsy reports, ever. An elegant review is available for those of us who are perplexed by the diagnosis of indeterminate colitis [2].

Conclusion

Histology taken at ileocolonoscopy plays a central part in the diagnosis and management of IBD. Frequent and specific communication between clinician and pathologist is the best way to minimize the risk of erroneous conclusions being reached.

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Part 1 Investigating IBD in the 21st Century

3 Non-invasive diagnosis and assessment

ALEX J DI MAMBRO, ANA TERLEVICH & CHRIS PROBERT

LEARNING POINTS

Non-invasive diagnosis and assessment

- C-reactive protein remains an important diagnostic and monitoring tool
- Raised fecal calprotectin correlates strongly with disease activity, has been used as a screening test for IBD and may predict relapse
- The combination of perinuclear antineutrophil cytoplasmic antibody (pANCA) and antibodies to *Saccharomyces cerevisiae* (ASCA) may help differentiate ulcerative colitis from Crohn's disease, especially in children
- In the right hands, abdominal ultrasound identifies active IBD in the terminal ileum and colon
- Analysis of fecal volatiles and genetic mutations may in the future alter the way we diagnose, monitor and treat IBD.

Introduction

Non-invasive assessment of IBD is desirable from the patient's point of view, as it is relatively painless and has few complications. However, it is also desirable from the clinical perspective: patients with chronic disease should not be exposed repeatedly to ionizing radiation, nor to endoscopic investigations, because of the potential risks from such procedures. In addition, in some parts of the world, endoscopy services are becoming over-stretched due, for example, to demands for colorectal cancer screening. In this synopsis, we discuss non-invasive methods for diagnosing and assessing IBD.

C-reactive protein

C-reactive protein (CRP), principally produced by hepatocytes, is part of the acute phase response. It has a short half-life and is therefore a useful marker to detect and monitor disease activity in Crohn's disease [1]. A raised CRP is, of course, non-specific, but, like a raised platelet count, can point to the possibility of IBD in patients presenting to the clinic with diarrhea and/or abdominal pain. In UC the acute phase response of CRP is, for unknown reasons, only modest, and CRP is not as good a marker of disease activity except in severe relapses, when a CRP >45 mg/L during treatment indicates a high risk of colectomy (see Chapter 42) [2]. Interestingly, recent trials of biologic agents in patients with Crohn's disease have found that those patients with raised CRP tend to respond better than those without (see Chapters 23, 31).

Plasma viscosity

Plasma viscosity is sometimes used alone, or in conjunction with CRP, to assess disease activity in IBD but is also non-specific. It has been shown to correlate well with CRP in both UC and Crohn's disease; however, it has a low sensitivity for detecting active Crohn's disease, being within the normal laboratory range in 48% of those with active disease [3].

Calprotectin

Calprotectin is a calcium-binding protein secreted predominantly by neutrophils. Elevated fecal calprotectin levels

are found in many inflammatory diseases of the intestine [4] and have been proposed as a way of deciding which patients with diarrhea and abdominal pain need further investigation for IBD. Fecal calprotectin levels correlate strongly with IBD activity and may be used to predict relapse [5].

Serology – pANCA and ASCA

Recent papers have shown a strong association between certain antibodies and IBD.

Perinuclear antineutrophil cytoplasmic antibody (pANCA) is found in patients with rheumatoid arthritis, systemic lupus erythematosus, microscopic polyangitis, and also in IBD. The prevalence of pANCA is increased in patients with UC (30–80%) compared with healthy controls. In comparison, pANCA is found less commonly in patients with Crohn's disease (0–20%). In UC, pANCA appears independent of disease extent and activity; however, in Crohn's disease its presence has been associated with UC-like features [6]. pANCA can be subdivided according to which perinuclear antigen antibodies are directed against. In patients with UC, the antigen may be histone 1, but antibodies are not directed against proteinase 3, myeloperoxidase, elastase, lysozyme, or cathepsin G [7].

The prevalences of IgG and IgA antibodies to *Saccharomyces cerevisiae (ASCAs)* are increased in patients with Crohn's disease compared with controls and range from 35–76% [8]. Patients who are ASCA-positive are more likely to have disease of the ileum, or ileum and colon, than patients who are ASCA-negative. Furthermore, ASCA-positive patients have also been shown to be more likely to require ileocecal resection [9].

Combining pANCA with ASCA increases specificity. For example, in UC, pANCA alone has a sensitivity and specificity of 65% and 85%, respectively; however, when combined with a negative ASCA, the sensitivity is 57% and the specificity 97% [10]. The positive predictive value (PPV) is therefore increased from 74% to 92% when the antibodies are combined.

Combined pANCA and ASCA has also been used to increase diagnostic accuracy in categorizing indeterminate colitis. One recent study showed that pANCA-positive and ASCA-negative patients with indeterminate colitis often progressed to a diagnosis of UC (PPV 64%), whereas those who were pANCA-negative and ASCA-positive were more likely to have CD (PPV 80%) [11].

Although pANCA alone is unlikely to provide the basis for a non-invasive screening test for IBD, it appears that in combination with ASCA it may have some adjuvant uses in differentiating Crohn's disease from UC, in categorizing indeterminate colitis, and possibly in determining disease pattern in Crohn's disease.

Recently, two new potential marker antibodies have been described: OmpC and I2. The low sensitivity of the antibodies to detect either Crohn's disease or ulcerative colitis means they are unlikely to have a diagnostic role [12], but they may be useful in screening for a fistulizing/stenotic phenotype with Crohn's disease as they are strongly associated with this pattern in children ($p < 0.006$ and < 0.003 for OmpC and I2, respectively [13].

Abdominal ultrasound

Abdominal ultrasound offers a simple, accessible, and non-invasive method of detecting and monitoring IBD (in particular Crohn's disease) and yet, at least in the UK, it is under-utilized. It has an overall accuracy of 89% in identifying active terminal ileal and colonic Crohn's disease (see Chapter 4) [14]. Doppler sonography, with or without contrast, is a newer, non-invasive method of assessing the hyperdynamic splanchnic and mesenteric blood flow that occurs in active inflammation. It can detect early mucosal and transmural inflammatory lesions. Furthermore, repeated quantification of mesenteric blood flow is claimed to enable the prediction of relapse at 6 months after steroid-induced remission [15]. (The role of magnetic resonance imaging [MRI] is discussed in Chapter 4.)

Analysis of fecal volatiles

Some patients with IBD have observed that the gas they emit per rectum during periods of disease activity smells different to that emitted when their disease is quiescent. Recently, we have investigated the composition of gas emitted from stool samples to explore this observation further and have found that the volatile compounds of such gas are different from those found in healthy volunteers. Furthermore, the gas produced by such stool samples can be used to distinguish between UC and Crohn's disease. This observation may lead to a novel diagnostic test.

However, the technique is still under evaluation and these results need to be reproduced in larger series before its usefulness for non-invasive diagnosis or monitoring of IBD can be determined.

Genetic mutations and IBD

The first gene to be identified as a risk factor for Crohn's disease is the *NOD2/CARD15* gene on chromosome 16 (see Chapter 24). Mutations of the gene are significantly more common in patients with Crohn's disease than in healthy controls. However, although the odds ratio is impressive, the genetic mutations are present in fewer than half of the patients studied [16,17]. At present, screening for these genes or other mutations plays no part in the diagnosis or monitoring of IBD [18].

Conclusions

At present, CRP and plasma viscosity remain the only widely available means of non-invasive monitoring of IBD. Fecal calprotectin looks promising as a diagnostic pointer towards IBD; it has the advantage of being a test of luminal disease and is therefore unlikely to be influenced by extra-intestinal disease processes. pANCA and ASCA may have a role in distinguishing Crohn's disease from UC and, potentially, IBD from other gastrointestinal disorders. Ultrasound warrants further investigation as a non-invasive technique for both diagnosing and monitoring Crohn's disease. Analysis of fecal volatiles is still at an early stage of development but also appears promising. Genetic screening is unlikely, in the foreseeable future, to be used to make a diagnosis of IBD.

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Part 1 Investigating IBD in the 21st Century

4 What is the best way to image perianal Crohn's disease?

VIKRAM A SAHNI & ALISON MCLEAN

LEARNING POINTS

Imaging pelvic Crohn's disease

- Perianal fistulae associated with Crohn's disease are often complex and tend to recur if the full extent is under-diagnosed at presentation
- Magnetic resonance imaging (MRI) and endoanal ultrasound (with or without hydrogen peroxide) are the investigations of choice
- MRI has superior contrast resolution and can identify deep extensions of complex perianal disease

Introduction

Pelvic Crohn's disease encompasses a spectrum of conditions including perianal skin tags, fissures, ulcers, and perianal abscesses and fistulae. Six to 34% of patients develop anal fistulae [1] and the diagnosis and treatment of these fistulae can be particularly challenging.

Although simple perianal fistulae can be identified at examination under anesthesia (EUA) and then treated successfully without the need for diagnostic imaging [2], fistulae associated with Crohn's disease are frequently complex with secondary extensions and ramifications. Failure to appreciate the complexity of such fistulae at EUA could result in incomplete treatment and may be responsible for the high rate of recurrence [3].

Several imaging modalities have been employed to delineate fistulous tracks, each with advantages and limitations. Fistulae should be classified as described by Parks *et al.* [4] to provide the surgeon with a roadmap which should minimize both operative trauma to the anal sphincters and subsequent recurrence.

Imaging

Contrast fistulography has historically been used to delineate fistula anatomy. This involves cannulating the external opening and injecting water-soluble contrast material under X-ray control. However, the technique has been shown to be unreliable, with an accuracy of only 16% [5]. It gives little information about the immediate anatomic relations especially to the sphincter mechanism and levator plate. The complete extent of complex fistulae and deep abscesses may not be identified if they fail to fill with contrast.

Although valuable in the overall assessment of complex transmural Crohn's disease, **computed tomography (CT)** has major limitations in the evaluation of perianal disease. The density of the anal sphincter, levator muscle, active fistulae, and fibrotic tracks on CT images are very similar, so that it is difficult to differentiate between them unless the fistula has been outlined by air or contrast [6].

CT has a role in the guidance of drainage of deep pelvic abscesses. It is widely available and allows a safe approach for drainage in an area where multiple intervening structures must be avoided. A transabdominal or transgluteal approach may be used [7].

Anal endosonography uses a high-frequency endoanal probe (typically 10 MHz) to evaluate sphincter anatomy

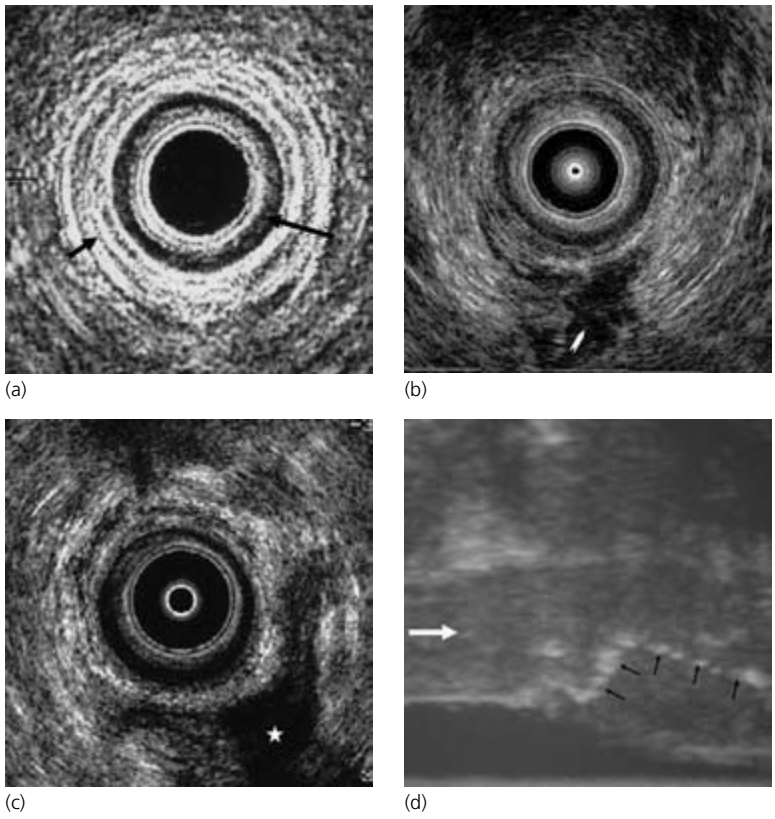

FIG 4.1 (a) Patient 1. Endoanal ultrasound demonstrating normal sphincter anatomy at the level of the mid anal canal (internal anal sphincter, long black arrow; external anal sphincter, short black arrow). (b) Patient 2. Endoanal ultrasound demonstrating posterior perianal fistula at the level of the mid anal canal (white arrowhead). (c) Patient 3. Endoanal ultrasound demonstrating posterior perianal collection at the level of the upper anal canal (white star). (d) Patient 4. Transrectal longitudinal ultrasound demonstrating thickened rectal wall (white arrow) with fistulous track (black arrows) extending above anal sphincter in rectal wall. The track is hyperreflective due to the presence of air within it. Fig. 4.1(a–c) courtesy of Dr. Mark Scott, Centre for Academic Surgery, Barts and The London, Queen Mary's School of Medicine and Dentistry, London, UK.

and provide high-resolution images of the internal and external sphincter. The internal sphincter appears as a hyporeflective ring while the external sphincter is of mixed reflectivity. Fistulous tracks appear as areas of low reflectivity unless they contain air, in which case they are hyperreflective (Fig. 4.1).

The advantage of anal endosonography is that it allows rapid evaluation in real time with no use of ionizing radiation. However, its primary limitation is the limited field of view it provides, which results in suboptimal visualization of the ischiorectal fossa and the supralevator area. This can lead to abscesses and fistulae being missed and, as a consequence, a high recurrence rate [8]. To compound this problem, endosonography cannot differentiate fistulae from scar tissue. Finally, in a proportion of patients with perianal inflammation, an endoanal probe cannot be tolerated because of anal stenosis or pain.

The advent of contrast-enhanced endosonography using hydrogen peroxide has improved the accuracy of the technique [9]. Hydrogen peroxide is introduced into the fistula track by cannulating the external orifice with an intravenous cannula. Within the fistula it generates small air bubbles which have a bright hyperreflective appearance.

The recent development of three-dimensional endoanal ultrasonography allows the axial images obtained from routine endoanal ultrasound to be reconstructed in the coronal and sagittal planes. West *et al.* [10] have shown that this technique, when combined with hydrogen peroxide, is comparable to endoanal MRI in detecting non-Crohn's perianal fistulae. Its capabilities in Crohn's disease are yet to be evaluated.

Some of the limitations of endoanal ultrasound can be overcome by using transcutaneous perianal ultrasound (PAUS) or transvaginal ultrasound. These two techniques, used in conjunction, allow for a larger field of view. In addition, they may be used when an endoanal probe cannot be tolerated. Wedemeyer *et al.* [11] have shown that transcutaneous PAUS has comparable sensitivity to MRI in detecting perianal fistulae and/or abscesses, yet is well tolerated and requires no special equipment.

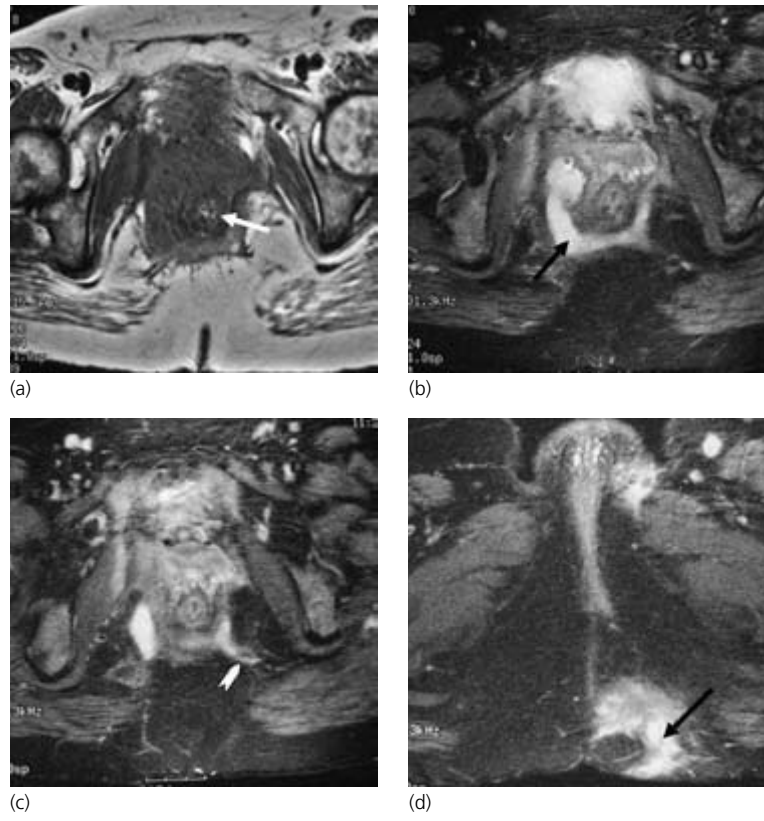

FIG 4.2 Patient 5. (a,b) T1 and Short Tau Inversion Recovery magnetic resonance imaging (STIR MRI) at the same level demonstrating anal sphincter mechanism (white arrow) and associated posterior horseshoe abscess (black arrow). The abscess involves both ischiorectal fossae. (c) STIR MRI demonstrating fistulous track extending to the left buttock (white arrowhead). (d) STIR MRI demonstrating left buttock abscess (black arrow).

Magnetic resonance imaging is a well-established technique for imaging perianal involvement in Crohn's disease. The value of the technique was first appreciated by Koelbel *et al.* [12], who imaged a small series of Crohn's patients with abdominopelvic fistulae. No absolute consensus of technique exists. However, most centers use a combination of T1, T2 (with or without fat suppression) and Short Tau Inversion Recovery (STIR) sequences in the axial and coronal plane. The T1 sequences provide anatomic information regarding the sphincter mechanism. The T2 and STIR sequences demonstrate the fistula track as high signal (Fig. 4.2).

Enhanced accuracy can be achieved by including imaging in the sagittal plane, instilling saline into the fistula track, or acquiring dynamic enhanced images with intravenous gadolinium.

The advantages of MRI are that it provides high soft tissue contrast resolution with true multiplanar capability. In addition, the wide field of view and lack of ionizing radiation make it attractive in young patients who may require multiple investigations [13].

The majority of MR examinations are acquired using a phased array torso receiver coil. However, endoanal receiver coils have been developed, and these provide excellent anatomic detail of the anal sphincters and the internal openings of fistulae [14]. The limitations are similar to those of endoanal ultrasound: a small field of view and poor patient tolerance in patients with extensive and painful perianal disease. In patients with extensive or complex pelvic disease, additional examination with a phased array torso coil is mandatory. Without this adjunct, the full extent of involvement would be missed, especially in the supralevator and ischiorectal compartments.

An extension of the role of MRI has been to assess the effects of antitumor necrosis factor, infliximab, on perianal Crohn's disease. Although external orifices stop draining after infliximab treatment, MRI has shown that fistula tracks often persist with residual inflammation. This has

important implications for fistula recurrence and abscess formation and can guide further treatment [15].

Evidence and conclusions

In the assessment of pelvic Crohn's disease, MRI, and endoscopic ultrasound appear to be the investigations of choice.

Two prospective trials have compared these techniques with surgical EUA. Orsoni *et al.* [16] found rectal endoscopic ultrasound to be the most sensitive modality. The agreement of ultrasound and MRI with surgical evaluation of perianal fistulae was 82% and 50%, respectively. Schwartz *et al.* [17] found all three techniques had an accuracy of over 85%. By combining any two procedures the accuracy improved to 100%. The low agreement between MRI and EUA in the former study may be because a whole body coil was used rather than a phased array coil which provides thinner slices and better spatial resolution. Another major difference in the studies was that Orsoni *et al.* [16] used EUA as the gold standard. This may not have been appropriate given its known potential for underestimating the extent of disease. In contrast, Schwartz *et al.* [17] used a consensus opinion of all three techniques to establish the gold standard.

The preferred examination will depend on local expertise, the facilities available, and patient tolerance. Each case should be assessed individually and a combination of techniques may be required.

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Clinical Dilemmas in Inflammatory Bowel Disease
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Part 1 Investigating IBD in the 21st Century

5 Surveillance colonoscopy in UC: alternatives and ways to improve outcome

MARK LUST & WILLIAM CONNELL

LEARNING POINTS

Surveillance colonoscopy in UC

- Colonoscopy with multiple random biopsies is currently the most widely used method of cancer surveillance in UC, but its overall efficacy and cost-effectiveness have not been substantiated
- Alternatives requiring further evaluation include:
  - prophylactic proctocolectomy
  - chemoprophylaxis with 5-aminosalicylic acid (5-ASA), folic acid and/or ursodeoxycholic acid
  - close clinical supervision
  - biomarkers such aneuploidy and p53
  - chromoendoscopy and magnifying endoscopy

Cancer risk in UC

Patients with UC face an increased risk of developing colorectal cancer (CRC), especially those with long-standing, extensive disease. The cumulative risk for cancer is estimated to be 2% at 10 years, 8% at 20 years, and 18% at 30 years [1]. Expressed in a different way, the lifetime prevalence of CRC in any patient with UC is 3.7%, increasing to 5.4% among individuals with pancolitis [1]. Individuals with extensive colitis are at greater risk of developing cancer than those with left-sided colitis, whereas the cancer risk in patients with proctitis is similar to that of the general population [2]. CRC is also increased among UC patients with coexisting primary sclerosing cholangitis [3], and possibly those with a family history of bowel cancer [4]. Recently, an important study from St. Mark's Hospital showed that active colonic inflammation represents a strong risk factor for the development of colorectal neoplasia in colitis [5]. The same group subsequently showed that macroscopic colonoscopic features helped predict the neoplasia risk in UC, and those with a normal-looking colon had a similar risk of developing colon cancer over 5 years of follow-up to the general population [6].

Endoscopic surveillance

Because most cancers complicating colitis are preceded by dysplasia, endoscopic surveillance has been recommended as a means to identify patients at imminent risk of carcinoma or to detect established cases of malignancy at an early and curable stage. Endoscopic surveillance involves regular (1–2 yearly) colonoscopic examinations of the entire bowel during which time multiple, random biopsies from flat mucosa or targeted biopsies from elevated or suspicious lesions are obtained. If dysplasia is detected, and confirmed by a separate pathologist, the predictive value of developing cancer is sufficiently high to justify prophylactic surgery [7]. Endoscopic surveillance is generally recommended in patients with extensive colitis or primary sclerosing cholangitis, usually commencing 8–10 years after disease onset, although patients with left-sided colitis may be included in similar programs starting 10–15 years after disease onset.

Although endoscopic surveillance is beneficial to many patients, its overall efficacy and cost effectiveness has never

been substantiated. In particular, it does not always prevent the development of advanced cancer, and the exercise is costly, inconvenient, and requires considerable administrative effort. Accordingly, the overall value of endoscopic surveillance has been questioned, and alternative options proposed to manage the cancer risk in colitis [8].

Alternatives to endoscopic surveillance

Prophylactic proctocolectomy

Prophylactic proctocolectomy offers the best means to eliminate the risk of cancer, and this option should be seriously considered in those at highest risk of developing cancer. However, surgical resection of the large bowel is a major undertaking which may be associated with the development of various postoperative complications including pouchitis. Not surprisingly, many patients are unwilling to agree to this option, especially when their health is otherwise satisfactory.

Chemoprophylaxis

There is evidence that 5-aminosalicylic acid (5-ASA) therapy may confer protection against the development of CRC in IBD patients [9–11]. In contrast to most series, a population-based study from Denmark showed no increase in the cancer rate among patients with IBD, and a possible reason for this observation was the widespread use of maintenance 5-ASA therapy [9]. A retrospective case–control study showed that mesalazine in a dosage of 1.2 g/day or more reduced the risk of cancer by 81% in patients with UC [10], and a separate case–control analysis also suggested that sulfasalazine therapy may reduce the risk of CRC in UC [11]. However, these results differ from a Canadian population-based study which did not confirm any definite chemopreventative effect of 5-ASA therapy [12]. It remains unclear if any anticancer effect from 5-ASA is purely due to a reduction in colonic inflammation or secondary to an induction of apoptosis and inhibition of cellular proliferation [8]. Other therapeutic agents with reported anticancer properties in IBD include folic acid, ursodeoxycholic acid (in those with coexisting primary sclerosing cholangitis), butyrate, and conjugated linoleic acid [8].

Clinical supervision

When UC patients present with symptoms of cancer, the tumor is usually diagnosed at an advanced stage when the prognosis is poor [13]. Therefore, a practice of clinical supervision and investigating new symptoms seems hazardous for UC patients, even if 5-ASA therapy is routinely used. Most patients who are informed of the association between colitis and cancer are not satisfied with this option.

Biomarkers

One of the limiting factors of dysplasia is that the diagnosis of dysplasia can be difficult to make in the presence of inflammation, and that considerable inter- and intra-observer variability applies [7]. An objective molecular marker that is reliably predictive of malignancy would be desirable to complement dysplasia in clinical practice. Like sporadic CRC, the major carcinogenic pathways leading to colitis-associated cancers involve chromosomal instability, microsatellite instability, and hypermethylation. However, the timing and frequency of key genetic changes are different, and abnormalities in these molecular pathways may be demonstrated in inflamed colonic mucosa even before any histologic evidence of dysplasia or cancer. Various markers that appear to indicate a subsequent risk of developing dysplasia or cancer include aneuploidy, p53, and mucin-associated sialyl Tn antigen [14]. There is insufficient evidence at present to support the use of these markers in clinical practice.

Chromoendoscopy and magnifying endoscopy

A major drawback of endoscopic surveillance is the limited ability to detect the presence of dysplasia from random colonic biopsies. If dysplasia was visible to the endoscopist, targeted biopsies could be obtained, thereby enhancing the diagnostic yield of endoscopic surveillance. Using a magnifying endoscope or chromoendoscopy (in which the colon is sprayed with indigo carmine or methylene blue) allows the endoscopist to recognize slight irregularities to the mucosal surface that cannot be appreciated by conventional endoscopy. Obtaining targeted biopsies from elevated or suspicious regions appears to be more accurate and time effective than a practise of taking large numbers of random, non-targeted biopsies [15,16].

Conclusions

In spite of its imperfections, endoscopic surveillance remains an effective means of reducing the cancer risk in most UC patients who do not wish to undergo prophylactic surgery. In future, however, patients may be stratified according to individual risk, and the conduct of surveil-

lance streamlined to reflect the level of risk. In this way, the development of advanced cancer can hopefully be minimized, and cost reduced. If the pivotal association between disease activity and CRC can be substantiated, this observation promises to significantly influence the way in which endoscopic surveillance is practiced. For example, intensive surveillance (6–12 monthly) with endoscopic spraying and magnifying endoscopy may be appropriate among patients with chronically active extensive disease or those with coexisting primary sclerosing cholangitis. In contrast, patients with persistently inactive disease could undergo colonoscopic examinations less regularly, possibly 5 yearly. In those with active inflammation confined to the distal colon and in whom no other risk factor for bowel cancer applies, it may be reasonable to simply undertake annual flexible sigmoidoscopy (making sure that that the upper level of disease is reached), and colonoscopy every 5 years. Eventually, new biomarkers may supplant dysplasia as a means of predicting malignancy, but until this time the use of 5-ASA compounds should be encouraged to offer additional protection against the development of CRC.

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