

Review article: colorectal cancer surveillance in ulcerative colitis – what should we be doing?

A. OBRADOR, D. GINARD & L. BARRANCO

Gastroenterology Department, Hospital Son Dureta, IUNICS Universitat de les Illes Balears, Palma, Mallorca, Spain

Correspondence to:
Dr A. Obrador, Servei de Digestiu
Hospital Son Dureta, Andrea Doria 55,
07014 Palma, Mallorca, Spain.
E-mail: obrador@hsd.es

Publication data

Submitted 28 June 2006

Accepted 28 June 2006

SUMMARY

Different societies have published guidelines for colorectal cancer (CRC) surveillance in ulcerative colitis (UC). While it would seem that most gastroenterologists and endoscopists agree with these guidelines, different studies have shown that in clinical practice, the concept of dysplasia is not fully understood, and therefore, the guidelines are not always followed. According to some studies, the reason why gastroenterologists do not follow the recommendations is inadequate education.

The main advance in recent years in this subject is in endoscopic diagnosis of dysplasia. The magnification and chromoendoscopy allow targeted biopsies to be taken. Some studies indicate that nontargeted biopsies are not useful in ruling out dysplasia. It is also important to realize that most dysplasia is visible in conventional colonoscopy. In colonoscopy, it is not only significant to detect dysplasia-associated lesions or masses; the endoscopist should also be trained to detect, in the course of conventional exploration, subtle changes in colour or in mucosal surfaces that imply dysplasia.

Adherence to guidelines had been extensively assessed in other disease conditions (asthma, hypertension, etc.). According to our knowledge there are no such data regarding CRC surveillance in UC.

Some barriers that may affect physicians include: (i) knowledge (lack of awareness or lack of familiarity); (ii) attitudes (lack of agreement, lack of self-efficacy, lack of outcome expectancy, or the inertia of previous practice) and (iii) behaviour (external barriers).

In conclusion, we need new guidelines for CRC surveillance in UC, which must take into account the advances in risk factors of dysplasia and new technologies to study colon dysplasia.

Aliment Pharmacol Ther 24 (Suppl. 3), 56–63

'The important thing in science is not so much to obtain new facts as to discover new ways of thinking about them'

Sir William Bragg (1862–1942)

INTRODUCTION

Different societies have published guidelines for the surveillance of colorectal cancer (CRC) in ulcerative colitis (UC).¹⁻³ These guidelines are very similar and very few variations are observed. It seems that the majority of gastroenterologists and endoscopists agree with these guidelines, and it is difficult to find critical reviews on the surveillance of CRC in UC.⁴ However, in clinical practice, many barriers exist to the adherence to these guidelines. Recently, some endoscopic techniques have been introduced for the surveillance of patients suffering from UC, but the guidelines have not incorporated these new advances. In this review, we comment on the last bibliography of this topic, bearing in mind the above quotation.

GUIDELINES, DYSPLASIA AND ADHERENCE

The guidelines regarding the surveillance of CRC in UC can be summarized as follows: (i) Regular surveillance should begin after 8–10 years for pancolitis and after 15–20 years for left-sided disease; (ii) There should be a decrease in the screening interval with increasing disease duration; (iii) Two to four random biopsy specimens, every 10 cm, should be taken from the entire colon, with additional samples of suspicious areas and (iv) Patients with primary sclerosis cholangitis represent a subgroup at higher risk.¹⁻³

Figure 1 illustrates some results of gastroenterology interview studies about dysplasia and surveillance practices of CRC in UC. The first study, performed in the United States, shows that only 19% of respondents correctly identified the definition of dysplasia.⁵ This

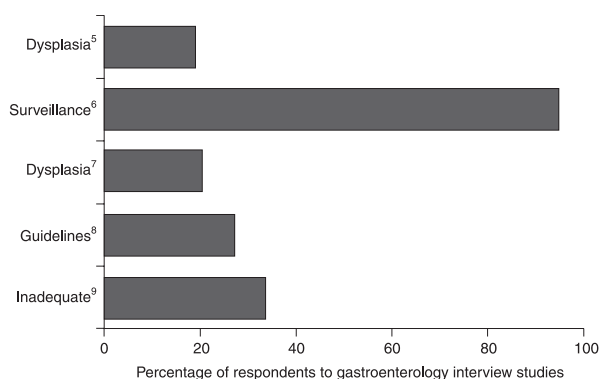


Figure 1. Gastroenterology studies of dysplasia and colorectal cancer surveillance.

was a survey study performed on members of two regional gastroenterology associations. More respondents (48%) correctly defined high-grade dysplasia specifically, compared with only 16% who correctly defined low-grade dysplasia. The majority of respondents (69%) recommended colectomy when high-grade dysplasia was diagnosed, yet nearly one third of respondents pursued continued surveillance in this setting.

The second study was performed in the United Kingdom, and the majority – 94% of consultants – practices cancer surveillance in UC, but this figure is distorted with the knowledge that this surveillance was not performed in a systematic way.⁶ Only 53% of British gastroenterologists in this study advised immediate colectomy when a patient had high-grade dysplasia.

The third study was performed more recently in New Zealand.⁷ A postal survey assessed the colonoscopist's understanding of how and why surveillance colonoscopy is undertaken and their interpretation of the results of this procedure. Of the 196 physicians and surgeons surveyed, 180 responded (92%). The results show that only 20% of respondents correctly defined dysplasia. There were differences in responses between specialist groups in this study, with colorectal surgeons most likely to correctly define dysplasia and appreciate the significance of low-grade dysplasia.

The fourth study was presented at the last digestive disease week and was performed in the Netherlands.⁸ A questionnaire was sent to all gastroenterologists in the Netherlands. Of 244 (61%) gastroenterologists, 148 responded. The four-quadrant biopsy protocol (every 10 cm, 30–40 biopsies in total), as recommended by the American Gastroenterological Association (AGA) was followed by 41% of the gastroenterologists, while 52% of the gastroenterologists took only 2–4 biopsies per segment and 6% used no specific biopsy protocol at all. This resulted in less than 30 biopsies per colonoscopy in 73% of the gastroenterologists. The AGA guidelines were followed by only 27% of gastroenterologists. The authors of this study indicated that they suspected this deviation from the guidelines to be a general phenomenon in clinical practice that was not only restricted to the Netherlands.

The last study on Figure 1 was recently published.⁹ This study analysed a small group of 67 consecutive patients suffering from inflammatory bowel disease (IBD), to determine whether patients were receiving optimal care. Three of nine (33%) were receiving inadequate surveillance of CRC.

The explanation for this low adherence to guidelines and for not knowing the concept of dysplasia is simple: 'gastroenterologists remain confused regarding the definition and implication of dysplasia. Their call for the education of the gastroenterology (and pathology) community is well substantiated'¹⁰ and 'it would appear that continued education of gastroenterologists concerning the many aspects and pitfalls of surveillance is needed'.⁶ 'The reason (for inconsistencies) may be a lack of education or, more likely, a lack of evidence to support an effective (including cost-effective), reliable surveillance algorithm for UC'.¹¹ In short, the problem appears to be the education of gastroenterologists.

Recent advances in the risk of cancer and the diagnosis of dysplasia in ulcerative colitis

Table 1 shows the main risk factors associated with CRC in UC.¹² The severity of inflammation was not considered a risk factor for CRC in UC until recently. A good review of this topic was recently published.¹³ A case-control study (68 cases, 136 controls) of patients with long-standing extensive UC was devised to examine the various potential risk factors for neoplasia.¹⁴ A univariate analysis showed a highly significant correlation between the colonoscopic [odds ratio (OR), 2.5; $P = 0.001$] and histological (OR, 5.1; $P < 0.001$) inflammation scores and the risk of colorectal neoplasia. In a multivariate analysis, only the histological inflammation score remained significant (OR, 4.7; $P < 0.001$). The authors concluded that in

Table 1. The importance of various risk factors in the development of cancer in ulcerative colitis. (Modified from Eaden and Mayberry.¹² Reprinted with permission from Elsevier.)

Risk factor	Relative importance
Extent of colonic involvement	++++
Long disease duration	++++
Severity of inflammation	+
Young age at disease onset	++
Geographical location	+
Treatment with aminosalicylates	+
Folic acid supplementation	+
Presence of stricture	++
Presence of primary sclerosing cholangitis	+++
Positive family history of sporadic CRC	+

long-standing extensive UC, the severity of colonic inflammation is an important determinant of the risk of colorectal neoplasia. Endoscopic and histological grading of inflammation could allow better risk stratification for surveillance programs.

Another study compared gross vs. microscopic pancolitis as a risk factor for the occurrence of neoplasia in UC.¹⁵ This study shows that UC-related neoplasia can occur in areas of the colon not grossly involved with colitis, although it did not occur in any patients without microscopic pancolitis. To devise rational cancer surveillance guidelines, further studies are needed to determine the risk of colitis-related neoplasia in patients with microscopic pancolitis but limited gross disease. Nevertheless, there are some experimental data to support the clinical observations.¹⁶

Two recent studies on the progression of low-grade dysplasia show divergent results. The methodology of both studies was very similar. The first was carried out in the United States.¹⁷ The authors reviewed the medical histories, colonoscopic findings and surgical and pathology reports of 46 patients with UC diagnosed with flat low-grade dysplasia in a surveillance colonoscopy. Among these 46 patients, there were seven cases of CRC, five of which were stage B or higher. Unexpected advanced neoplasia occurred in 4 of 17 (23.5%) patients who underwent colectomy for flat low-grade dysplasia. The study concluded that the discovery of flat low-grade dysplasia during UC surveillance is a strong predictor of progression to advanced neoplasia, and early colectomy should be recommended for such patients.

The second study was carried out in the United Kingdom.¹⁸ One hundred sixty patients with long-standing extensive UC were recruited for annual colonoscopic surveillance and 40 developed low-grade dysplasia at some stage. The study reported the outcome of this cohort 10 years after the original study ended. Of the 128 patients still alive and with an intact colon at the end of the study, 2 were not traceable, 29 had low-grade dysplasia and 97 had no dysplasia (controls). After 10 years, high-grade dysplasia or CRC developed in 3/29 patients with low-grade dysplasia (10%) and in 4/97 controls (4.0%). Kaplan-Meier analysis from 1991 to death or colectomy did not show a statistically significant difference between the two groups (log rank test; $P = 0.63$).

A divergent conclusion arises from the European study in relation to the American study: low-grade dysplasia diagnosis is not sufficiently reliable to justify

prophylactic colectomy, and conservative management of established low-grade dysplasia cases should not be ruled out. So, for the practical gastroenterologist, which message should be taken into account? In our opinion, it is very important to know the natural history of dysplasia, especially low-grade dysplasia, because the results of these two studies are not biologically plausible.

Histological diagnosis of dysplasia had some known drawbacks. The interobserver agreement is fair in some studies.¹⁹⁻²¹ It is important to remember that colonic biopsies had to be taken in quiescent UC, because the presence of inflammation could be misleading. Two lesser known aspects are:

1. Histological changes associated with the use of intravenous ciclosporin in the treatment of severe UC may mimic dysplasia.²² The aim of this study was to describe the histological changes in patients who received iv ciclosporin and steroids (23 colectomy specimens, for 11 of which pre-ciclosporin histological sections were available) compared with those treated with iv steroids alone (10 colectomy specimens). Although villous transformation and epithelial regeneration may be seen in UC, they are more frequent and more severe in those patients who received iv ciclosporin and iv steroids, when compared with controls who received iv steroids alone. These histological changes may mimic dysplasia. Increased awareness of this potential mimic of dysplasia is crucial for patient management in the countries that used iv ciclosporin for treating severe UC.

2. Reactive changes associated with ischaemic colitis may also mimic dysplasia.²³ This study described the retrospective analysis of surgical pathology files with the diagnosis 'ischaemia, bowel'. All cases were studied for reactive or reparative atypical changes. Reactive atypical (pseudodysplastic) changes were found in 8 of 28 cases of ischaemic bowel. The clinical history did not indicate ischaemic colitis in six of eight cases. In three cases, neutrophils in the lamina propria or acute cryptitis and crypt abscesses, which suggested IBD, were noted. Ischaemic changes in the bowel may produce reactive epithelial changes with sufficient atypia to simulate dysplasia. These may be associated with histological changes that simulate IBD, specifically UC. As in most cases, even the clinician is not sure whether the patient has ischaemia or IBD, and because histological changes of the latter may occur in ischaemic bowel, there is a danger that the atypical reactive ischaemic chan-

ges could be interpreted as true dysplasia that occurs in IBD.

ENDOSCOPIC DIAGNOSIS OF DYSPLASIA: MAGNIFICATION AND CHROMOENDOSCOPY

The main advance in recent years in this field is in endoscopic diagnosis of dysplasia. There are some good reviews about endoscopic diagnosis of dysplasia.²⁴⁻²⁷ We selected the most representative studies according to our personal criteria. The first refers to the importance of chromoendoscopy in taking targeted biopsies vs. nontargeted biopsies.²⁸ One hundred patients with long-standing extensive UC attending for colonoscopic surveillance underwent 'back-to-back' colonoscopies. During the first examination, visible abnormalities were biopsied, and quadrantic nontargeted biopsies were taken every 10 cm. Pancolonic indigo carmine (0.1%) was used during the second colonoscopic examination, and any additional visible abnormalities were biopsied. In 2904 nontargeted biopsies, no dysplasia was detected. In comparison, a targeted biopsy protocol with pancolonic chromoendoscopy required fewer biopsies (157), yet detected nine dysplastic lesions, seven of which were only visible after indigo carmine application. Careful mucosal examination aided by pancolonic chromoendoscopy and targeted biopsies of suspicious lesions may be a more effective surveillance methodology than taking multiple nontargeted biopsies. The conclusion of this study is clear: nontargeted biopsies are not useful for ruling out dysplasia.

In 2003, another important study was published using methylene blue chromoendoscopy (and magnification) in a randomized trial.²⁹ One hundred sixty-five patients were randomized to undergo colonoscopy or magnification colonoscopy with chromoendoscopy. More targeted biopsies were possible and significant intraepithelial neoplasia was detected in the chromoendoscopy group (32 vs. 10; $P = 0.003$). Sensitivity and specificity for differentiation between non-neoplastic and neoplastic lesions were 93%. The authors of this review concluded that chromoendoscopy with methylene blue is a novel tool for the early detection of intraepithelial neoplasia and CRC in patients with UC.

Recently, new guidelines were published, named SURFACE, for chromoendoscopy in UC.³⁰ These guidelines are shown in Table 2. The seven rules are (i) strict patient selection; (ii) unmask the mucosal surface; (iii) reduce peristaltic waves; (iv) full-length

staining of the colon; (v) augmented detection with dyes; (vi) crypt architecture analysis and (vii) endoscopic targeted biopsies.

New endoscopic technologies such as narrowband imaging, fluorescence endoscopy, optical coherence tomography and confocal laser endomicroscopy may improve the detection of early neoplastic lesions and may be able to guide biopsy sampling to relevant lesions in the gut. However, the clinical data are at present still limited.³¹ With preliminary results comparable to magnification and chromoendoscopy, it is possible that narrowband imaging will be introduced in the future as a surveillance tool in UC.^{32, 33}

Diagnosis of dysplasia with conventional colonoscopy

However, it is not always necessary to use chromoendoscopy. In a recent, retrospective study in which 525 patients underwent 2204 surveillance colonoscopies, it was concluded that most dysplasia is visible at conventional colonoscopy.³⁴ In 110 neoplastic areas, more than 75% were macroscopically visible. Almost 90% of neoplasias were macroscopically detected. This study has an important message for all gastroenterologists and endoscopists, and should encourage meticulous examination of the colon for mucosal abnormalities. It is not only important to detect dysplasia-associated lesions or masses at colonoscopy, but the endoscopist, in conventional exploration, must also be alert to subtle changes in colour or in the mucosal surface that imply dysplasia.

A 2005 study corroborates the importance of meticulous examination of the colon.³⁵ The aim of this study was to analyse the endoscopic factors in the diagnosis of dysplasia in IBD. This was a retrospective study performed with 635 patients who underwent surveillance colonoscopies. Using logistic regression analysis, it was observed that every additional minute in total colonoscopy time increased the flat dysplasia diagnosis rate by 3.5%. There was a significant correlation between median surveillance colonoscopy duration per endoscopist and flat dysplasia diagnosis rate. This study illustrated that longer procedure duration is significantly associated with the likelihood of diagnosis of dysplasia.

In some respects, the history of small flat colonic cancer lesions, first described by Japanese endoscopists, reminds us of the history of dysplasia in UC.³⁶⁻⁴¹ In recent years, they have suggested that early colorectal malignancies may arise as 'flat' or 'depressed' rather than as polypoid lesions. Such flat or depressed adenomas and adenocarcinomas have not been widely recognized in the West. At first, small flat colonic cancer was considered only a Japanese lesion. However, we now observe the same lesions in Europe and in America. The most important factor for diagnosis is learning to recognize this type of superficial small flat lesion. Special training is needed to detect depressed lesions, as these tend to be smaller than other lesions, and usually only appear as erythematous patches. Without this training, one author predicted that the colonoscopic screening protocols will fail to detect between 20% and 50% of all preventable cancers.³⁶

Table 2. Seven guidelines (SURFACE) for chromoendoscopy in ulcerative colitis (UC).³⁰ (Reproduced with permission from the BMJ Publishing Group)

- 1 *Strict patient selection:* Patients with histologically proved UC and at least 8 years duration in clinical remission. Avoid patients with active disease.
- 2 *Unmask the mucosal surface:* Excellent bowel preparation is needed. Remove mucus and remaining fluid in the colon when necessary.
- 3 *Reduce peristaltic waves:* When drawing back the endoscope, a spasmolytic agent should be used (if necessary).
- 4 *Full-length staining of the colon:* Perform full-length staining of the colon (panchromoendoscopy) in UC rather than local staining.
- 5 *Augmented detection with dyes:* Intravital staining with 0.4% indigo carmine or 0.1% methylene blue should be used to unmask flat lesions more frequently than with conventional colonoscopy.
- 6 *Crypt architecture analysis:* All lesions should be analysed according to the pit pattern classification. Whereas pit pattern types I-II suggest the presence of nonmalignant lesions, staining patterns III-V suggest the presence of intraepithelial neoplasias and carcinomas.
- 7 *Endoscopic targeted biopsies:* Perform targeted biopsies of all mucosal alterations, particularly of circumscribed lesions with staining patterns indicative of intraepithelial neoplasias and carcinomas (pit patterns III-V).

According to the conclusion of a prospective study, carried out to search for flat and depressed adenomas in a British population, using Japanese colonoscopic techniques, European colonoscopists require training in the recognition of flat, elevated and depressed lesions in order to detect colorectal malignancies in their early stages.³⁷

Based on the literature, it is important to realize that it is possible to detect dysplasia by colonoscopy using chromoscopy and magnification techniques, and also with conventional colonoscopy. But we must learn to recognize the dysplastic lesion. Picasso, a Spanish genius, once said: 'I don't search, I find'. But most gastroenterologists are not geniuses, and therefore, in colonoscopic exploration, we must (i) learn to recognize; (ii) perform many searches and (iii) find small lesions in patients suffering from extensive UC for more than 8 years.

Adherence to guidelines

Adherence to guidelines had been extensively assessed in other disease states (asthma, hypertension, etc.).⁴²⁻⁴⁵ According to our knowledge, there are no such data regarding CRC surveillance in UC. An extensive review revealed why physicians do not follow clinical practice guidelines.⁴⁶ After classifying possible barriers into common themes, the analysis found that the 293 questions about barriers included seven general categories of barriers. The barriers affected physician knowledge (lack of awareness or lack of familiarity), attitudes (lack of agreement, lack of self-efficacy, lack of outcome expectancy, or the inertia of previous practice), or behaviour (external barriers) (Figure 2). Another more recent study classified the barriers to physician guideline compliance.⁴⁷ The construct includes past behaviour (degree of change, past experiences, attitude and subjective norm); perceived behavioural control; and behavioural intention and behaviour. Knowledge

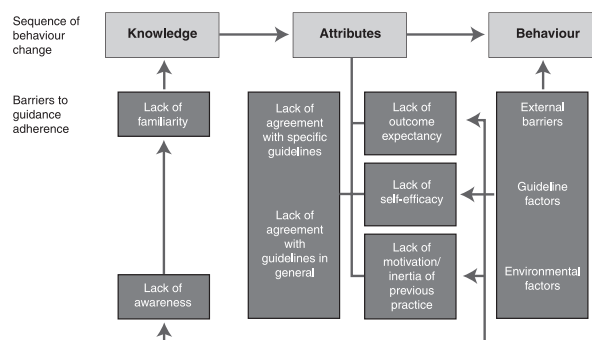


Figure 2. Barriers to physician adherence to practice guidelines in relation to behaviour change. (Modified from Cabana *et al.*⁴⁶ Reprinted with permission from the American Medical Association.)

is only one of a spectrum of barriers that affects physician adherence to guidelines.⁴⁸

In the process of creating new guidelines for surveillance of CRC in UC,⁴⁹ some topics that require investigation include natural history of dysplasia; best methods for teaching the importance of dysplasia; physician awareness of CRC in UC; capacity of endoscopy units to perform colonoscopy in indicated cases; implementation of new endoscopic techniques for diagnosing dysplasia and training of endoscopists to identify subtle changes in colonic mucosa.

CONCLUSION

In conclusion, we need new guidelines for the surveillance of CRC in UC. These guidelines must take into account inflammation as a risk factor and implement new technologies to study colon dysplasia. The effectiveness of any new guidelines must be scientifically proved. Investigations regarding the adherence of the gastroenterologists to the new guidelines/recommendations would be necessary, in order to ascertain their level of knowledge, their attitudes and behaviour.

REFERENCES

- Eaden JA, Mayberry JF. Guidelines for screening and surveillance of asymptomatic colorectal cancer in patients with inflammatory bowel disease. *Gut* 2002; 51 (Suppl. 5): V10-2.
- Barthet M, Gay G, Sautereau D, *et al.* Endoscopic surveillance of chronic inflammatory bowel disease. *Endoscopy* 2005; 37: 597-9.
- Itzkowitz SH, Present DH. Crohn's and Colitis Foundation of America Colon Cancer in IBD Study Group. Consensus conference: colorectal cancer screening and surveillance in inflammatory bowel disease. *Inflamm Bowel Dis* 2005; 11: 314-21.
- Moum B, Ekblom A. Ulcerative colitis, colorectal cancer and colonoscopic surveillance. *Scand J Gastroenterol* 2005; 40: 881-5.

5. Bernstein CN, Weinstein WM, Levine DS, Shanahan F. Physicians' perceptions of dysplasia and approaches to surveillance colonoscopy in ulcerative colitis. *Am J Gastroenterol* 1995; **90**: 2106–14.
6. Eaden JA, Ward BA, Mayberry JF. How gastroenterologists screen for colonic cancer in ulcerative colitis: an analysis of performance. *Gastrointest Endosc* 2000; **51**: 123–8.
7. Geary RB, Wakeman CJ, Barclay ML, *et al.* Surveillance for dysplasia in patients with inflammatory bowel disease: a national survey of colonoscopic practice in New Zealand. *Dis Colon Rectum* 2004; **47**: 314–22.
8. van Rijn AF, Samsom M, Oldenburg B. Adherence to surveillance guidelines for dysplasia and colonic carcinoma in ulcerative and Crohn's colitis patients in the Netherlands. *Gastroenterology* 2005; **128** (Suppl. 2): A-324 (Abstract).
9. Reddy SI, Friedman S, Telford JJ, Strate L, Ookubo R, Banks PA. Are patients with inflammatory bowel disease receiving optimal care? *Am J Gastroenterol* 2005; **100**: 1357–61.
10. Cohen RD, Hanauer SB. Surveillance colonoscopy in ulcerative colitis: is the message loud and clear? *Am J Gastroenterol* 1995; **90**: 2090–2.
11. Hanauer SB. Surveying surveillance: are gastroenterologists consistently inconsistent, inconsistently consistent, or poorly educated? *Gastrointest Endosc* 2000; **51**: 240–2.
12. Eaden JA, Mayberry JF. Colorectal cancer complicating ulcerative colitis: a review. *Am J Gastroenterol* 2000; **95**: 2710–9.
13. Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. *Am J Physiol Gastrointest Liver Physiol* 2004; **287**: G7–17.
14. Rutter M, Saunders B, Wilkinson K, *et al.* Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology* 2004; **126**: 451–9.
15. Mathy C, Schneider K, Chen YY, Varma M, Terdiman JP, Mahadevan U. Gross versus microscopic pancolitis and the occurrence of neoplasia in ulcerative colitis. *Inflamm Bowel Dis* 2003; **9**: 351–5.
16. Chen R, Rabinovitch PS, Crispin DA, Emond MJ, Bronner MP, Brentnall TA. The initiation of colon cancer in a chronic inflammatory setting. *Carcinogenesis* 2005; **26**: 1513–9.
17. Ullman T, Croog V, Harpaz N, Sachar D, Itzkowitz S. Progression of flat low-grade dysplasia to advanced neoplasia in patients with ulcerative colitis. *Gastroenterology* 2003; **125**: 1311–9.
18. Lim CH, Dixon MF, Vail A, Forman D, Lynch DA, Axon AT. Ten year follow up of ulcerative colitis patients with and without low grade dysplasia. *Gut* 2003; **52**: 1127–32.
19. Dixon MF, Brown LJ, Gilmour HM, *et al.* Observer variation in the assessment of dysplasia in ulcerative colitis. *Histopathology* 1988; **13**: 385–97.
20. Eaden J, Abrams K, McKay H, Denley H, Mayberry J. Inter-observer variation between general and specialist gastrointestinal pathologists when grading dysplasia in ulcerative colitis. *J Pathol* 2001; **194**: 152–7.
21. Odze RD, Goldblum J, Noffsinger A, Alsaigh N, Rybicki LA, Fogt F. Interobserver variability in the diagnosis of ulcerative colitis-associated dysplasia by telepathology. *Mod Pathol* 2002; **15**: 379–86.
22. Hyde GM, Jewell DP, Warren BF. Histological changes associated with the use of intravenous cyclosporin in the treatment of severe ulcerative colitis may mimic dysplasia. *Colorectal Dis* 2002; **4**: 455–8.
23. Zhang S, Ashraf M, Schinella R. Ischemic colitis with atypical reactive changes that mimic dysplasia (pseudodysplasia). *Arch Pathol Lab Med* 2001; **125**: 224–7.
24. Dekker E, Fockens P. Advances in colonic imaging: new endoscopic imaging methods. *Eur J Gastroenterol Hepatol* 2005; **17**: 803–8.
25. Herfarth H, Rogler G. Inflammatory bowel disease. *Endoscopy* 2005; **37**: 42–7.
26. Fefferman DS, Farrell RJ. Endoscopy in inflammatory bowel disease: indications, surveillance, and use in clinical practice. *Clin Gastroenterol Hepatol* 2005; **3**: 11–24.
27. Rutter M, Bernstein C, Matsumoto T, Kiesslich R, Neurath M. Endoscopic appearance of dysplasia in ulcerative colitis and the role of staining. *Endoscopy* 2004; **36**: 1109–14.
28. Rutter MD, Saunders BP, Schofield G, Forbes A, Price AB, Talbot IC. Pan-colonic indigo carmine dye spraying for the detection of dysplasia in ulcerative colitis. *Gut* 2004; **53**: 256–60.
29. Kiesslich R, Fritsch J, Holtmann M, *et al.* Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. *Gastroenterology* 2003; **124**: 880–8.
30. Kiesslich R, Neurath MF. Surveillance colonoscopy in ulcerative colitis: magnifying chromoendoscopy in the spotlight. *Gut* 2004; **53**: 165–7.
31. Kiesslich R, Hoffman A, Neurath MF. Colonoscopy, tumors, and inflammatory bowel disease—new diagnostic methods. *Endoscopy* 2006; **38**: 5–10.
32. Kuznetsov K, Lambert R, Rey JF. Narrow-band imaging: potential and limitations. *Endoscopy* 2006; **38**: 76–81.
33. Dekker E, Van Deventer S, Hardwick J, *et al.* The value of narrow band imaging for the detection of dysplasia in long-standing ulcerative colitis. *Gastroenterology* 2004; **126**: A77 (Abstract).
34. Rutter MD, Saunders BP, Wilkinson KH, Kamm MA, Williams CB, Forbes A. Most dysplasia in ulcerative colitis is visible at colonoscopy. *Gastrointest Endosc* 2004; **60**: 334–9.
35. Toruner M, Harewood GC, Loftus EV Jr, *et al.* Endoscopic factors in the diagnosis of colorectal dysplasia in chronic inflammatory bowel disease. *Inflamm Bowel Dis* 2005; **11**: 428–34.
36. Rembacken BJ. Flat and depressed colorectal neoplasia in England and Japan (Foundation for Promotion of Cancer, Japan and the British Council). *Jpn J Clin Oncol* 1997; **27**: 447.
37. Fujii T, Rembacken BJ, Dixon MF, Yoshida S, Axon AT. Flat adenomas in the United Kingdom: are treatable cancers being missed? *Endoscopy* 1998; **30**: 437–43.
38. Kobayashi K, Sivak MV Jr. Flat adenoma: are western colonoscopists careful enough? *Endoscopy* 1998; **30**: 487–9.
39. Rembacken BJ, Fujii T, Cairns A, *et al.* Flat and depressed colonic neoplasms: a prospective study of 1000 colonoscopies in the UK. *Lancet* 2000; **355**: 1211–4.
40. Church JM, Muto T, Appau K. Flat lesions of the colorectal mucosa: differences in recognition between Japanese and American endoscopists. *Dis Colon Rectum* 2004; **47**: 1462–6.
41. Soetikno R, Friedland S, Kaltenbach T, Chayama K, Tanaka S. Nonpolypoid (flat and depressed) colorectal neoplasms. *Gastroenterology* 2006; **130**: 566–76.
42. Ma J, Stafford RS. US physician adherence to standards in asthma pharmacotherapy varies by patient and physician characteristics. *J Allergy Clin Immunol* 2003; **112**: 633–5.

43. Nelson MR, Reid CM, Krum H, McNeil JJ. Factors influencing family physician adherence to hypertension treatment guideline recommendations on the initiation of pharmacotherapy: questionnaire survey. *Am J Cardiovasc Drugs* 2003; 3: 437–41.
44. Al Aqeel A, Mojiminiyi OA, Al Dashti R, Al Ozairi ES. Differences in physician compliance with guideline on lipid profile determination within 24 h after acute myocardial infarction. *Med Princ Pract* 2005; 14: 41–5.
45. Mosca L, Linfante AH, Benjamin EJ, *et al.* National study of physician awareness and adherence to cardiovascular disease prevention guidelines. *Circulation* 2005; 111: 499–510.
46. Cabana MD, Rand CS, Powe NR, *et al.* Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999; 282: 1458–65.
47. Maue SK, Segal R, Kimberlin CL, Lipowski EE. Predicting physician guideline compliance: an assessment of motivators and perceived barriers. *Am J Manag Care* 2004; 10: 383–91.
48. Ward MM, Vaughn TE, Uden-Holman T, Doebbeling BN, Clarke WR, Woolson RF. Physician knowledge, attitudes and practices regarding a widely implemented guideline. *J Eval Clin Pract* 2002; 8: 155–62.
49. Hurlstone DP, Sanders DS, Lobo AJ, McAlindon ME, Cross SS. Indigo carmine-assisted high-magnification chromoscopic colonoscopy for the detection and characterisation of intra-epithelial neoplasia in ulcerative colitis: a prospective evaluation. *Endoscopy* 2005; 37: 1186–92.