Leading article

Cancer surveillance in ulcerative colitis – a time for reappraisal

Patients who have had an attack of universal or extensive ulcerative colitis have a greater likelihood of developing colonic cancer than the normal population.[1–6] The enhanced risk begins about 10 years after the initial attack. Earlier reports exaggerated the danger of malignant change because they were based upon retrospective studies of patients who had been referred to specialised centres.[1 2 7] Recent population based studies suggest that the risk is considerably less.[1 8 9]

The recognition that ulcerative colitis has a malignant potential places a responsibility on clinicians to minimise or eliminate the risk that these patients will die from colonic cancer. One solution advocated is to perform colectomy 10 years after the initial attack.[10] This would virtually eliminate the possibility of cancer but most gastroenterologists and patients prefer a less radical approach, that of 'surveillance'.[11] The finding that in many cases, cancer could be predicted by the finding of dysplastic change in the rectal mucosa[12–14] has led to the view that the best method of surveillance must be regular colonoscopy, which permits the whole colon to be visualised, with target biopsy where appropriate. In addition a wide area of mucosa can be sampled for dysplastic change. It seems logical that patients who have had extensive or total ulcerative colitis should have regular annual colonoscopy starting eight to 10 years after the first attack of ulcerative colitis. If this is undertaken rigorously it is argued the risk of cancer will be minimised and when present, neoplastic lesions will be detected at an early stage and mortality from colorectal cancer will be greatly reduced. Over the past 12 years several large prospective studies have assessed this policy of colonoscopic surveillance. Most have concluded that it is the best way of managing this difficult problem but when these studies are critically analysed the case for colonoscopic surveillance is weaker than at first sight, and some commentators consider that the exercise is not cost effective and that when assessed on an 'intention to survey' basis they confer little benefit.[15–20]

Twelve studies of colonoscopic cancer surveillance in ulcerative colitis have been published in sufficient detail to analyse critically.[20–31] The stated intention in most of them was to undertake colonoscopic surveillance in all patients who had had total or extensive disease. Surveillance was usually started eight to 10 years after the initial attack. A total of 1916 patients were included and 92 cancers were reported. Of these 52 (57%) were Dukes's A or B, the remainder were Dukes's C or worse and cannot be counted as 'success' for the surveillance programmes. Of the 52 patients with Dukes's A and B cancer 11 were discovered at operation (or necropsy) the disease not having been identified before the operation, 17 were discovered as a result of suspicious appearances at barium enema or at sigmoidoscopy – that is, they were not discovered as a result of colonoscopic surveillance. Two cancers were found in operative specimens from patients operated on for low grade dysplasia (not an indication most clinicians would accept for advising colectomy). If these cases are excluded only 22 Dukes's A and B cancers (24%) were actually found by colonoscopy screening. Of these 22 cancers three were discovered in patients who were outside the accepted entry criteria for colonoscopic surveillance, being found either in patients with limited colitis or discovered before eight years had elapsed from the first attack. Eight cancers were found on 'screening' colonoscopy, compared with 'surveillance' colonoscopy, 'screening' being defined as the initial colonoscopy performed, usually on patients referred to the centre for the first time (often many years after the first attack of colitis) or after a period of defaulting from follow up. This group of patients may have presented to the clinic or have been referred to the clinic because of new symptoms, possibly because of the cancer itself. Of the 92 cancers identified in these studies therefore only 11 (12%) Dukes's A and B cancers were detected as a result of ongoing 'surveillance colonoscopy'. This result is disappointing and particularly so because the reports are from centres with a particular interest and expertise in managing ulcerative colitis.

The number of colonoscopies performed was recorded in 11 of 12 studies. In all, 3807 colonoscopies were performed to detect eight early cancers (as defined by the criteria outlined above) – that is, 1 per 476 examinations. It is difficult to justify the time and expense involved for such a small return. It can be calculated theoretically that screening the normal population in the 40–80 age group in England and Wales on a five yearly basis would yield a higher number of premalignant polyps or cancer than this.[20] Similar calculations have been made in the USA.[18] A recent prospective study in 210 asymptomatic subjects identified two Dukes's A cancers.[32] The identification of Dukes's A cancer at colonoscopy in patients positive on faecal occult blood testing is 1 per 18 colonoscopies.[33]

Surveillance studies cannot be criticised solely on the small number of early cancers identified. Patients operated on for dysplastic change may have been protected from developing cancer. Dysplasia in ulcerative colitis is a complex[34] and unsatisfactory concept. Firstly the diagnosis of dysplasia is not straight forward, and even experienced pathologists disagree as to whether a biopsy sample exhibits dysplastic change.[35 36] Secondly the clinical significance of dysplasia is unclear. Approximately 30% of ulcerative colitis associated cancers occur within a bowel where there is no dysplasia in the rest of the colon,[36] conversely most patients with dysplasia do not have cancer.[37–39]

Dysplasia is classified as 'low grade' or 'high grade'.[40] Eleven studies recorded the number of patients with low grade dysplasia. Seventy three cancers were found in 1656 patients without low grade dysplasia (4·4%) whereas 26 cancers were found in 313 patients with it (8%) and if dysplasia associated lesions or masses are excluded this falls to 6%. Two facts emerge, firstly nearly three times as many cancers occurred in patients without low grade dysplasia as with, and secondly the incidence of cancer in the two groups is similar. Further data that cast doubt on the significance of low grade dysplasia comes from a study[22] where the longterm likelihood of developing low grade dysplasia was recorded. By 40 years less than 20% of subjects remain free from low grade dysplasia (or worse). These data have been confirmed independently recently by others[20] and suggest that nearly all patients will eventually

develop low grade dysplasia or cancer if followed up for long enough. Finally, low grade dysplasia is inconsistent being present one year and absent the next. One recent paper[26] has argued that patients with low grade dysplasia should be followed up more carefully because of their increased risk. This advice was based on the finding that surveillance of low grade dysplasia had led to the recognition of neoplasm in seven (10%) of a group of 121 patients. Of these seven, however, only four had low grade dysplasia. Three of seven died from metastatic cancer, in a further two the colitis was confined to the left side of the bowel (not a group in which surveillance is usually undertaken). In the remaining two with low grade dysplasia the patients had had 17 and 20 colonoscopies respectively (an average of two colonoscopies each per year) a policy that few centres could undertake and few patients would tolerate.

Twelve studies recorded the presence of high grade dysplasia. Cancer was present in 93 of 2044 patients without high grade dysplasia (4·5%) whereas 35 were found in 101 patients with it (35%). It is impossible to assess in most cases whether the high grade dysplasia was found in association with the cancer (and was actually a superficial biopsy specimen from a well differentiated adenocarcinoma) or whether it was remote from it, nevertheless the finding of high grade dysplasia should alert the clinician to the high risk of concomitant cancer. Not all clinicians, however, have insisted on colectomy under these circumstances. In one series 25% of patients with high grade dysplasia had a negative colectomy specimen or colonoscopy on follow up,[23] in another paper seven of 14 were not operated on and remain 'under surveillance'.[30] Six of 15 were not operated on in a third study[29] and one of three in a fourth.[28]

In summary low grade dysplasia has little prognostic value, will eventually affect 80% of subjects, and comes and goes in the colitic population. High grade dysplasia does have serious implications but in practice does not always change management.

Why has the apparently logical concept of colonoscopic surveillance proved to be so disappointing? Careful scrutiny suggests that colonoscopic surveillance programmes themselves have actually been quite effective. Early cancers have been found in subjects who were prepared to undergo regular colonoscopy. The failures (extensive cancer) have usually occurred in subjects referred for the first time for colonoscopic surveillance (screening) having been discharged or having been lost to follow up before becoming eligible for surveillance, or alternatively they have arisen in defaulters or those who have moved away. Surveillance can be deemed a failure only on the basis of 'intention to survey'. Returning, however, to the patients who have had regular surveillance, the problem here is not that patients have been identified at a late stage, but that the amount of time, effort, and expense has yielded such insubstantial results – that is, eight early cancers among 3807 colonoscopies. Although the number of early cancers detected would rise if more patients were brought into the surveillance programme and patients were more avidly followed up to prevent defaulting and were given a colonoscopy more often, this would not improve the detection/colonoscopy ratio. Indeed more negative colonoscopies would be performed to detect a diminishing number of early cancers. As the effectiveness of colonoscopic surveillance in colitis as practised already is less than that obtained from colonoscoping the normal population it is hard to justify an even more aggressive approach.

Not only are colonoscopic surveillance programmes ineffective for most colitic patients, they may be positively disadvantageous. Patients under surveillance go through an unpleasant experience with bowel preparation. They lose time from their normal activities, the procedure itself is undignified and sometimes painful. Surveillance is a constant reminder to them that even without symptoms they have ongoing disease, and the worry of cancer is reinforced on a regular basis. These factors are possibly responsible for poor recruitment and compliance. Once having defaulted there is a chance that the subject will not return with the minor symptoms that would permit a neoplasm to be identified at an earlier stage. It is possible that the apparently higher incidence of cancer found in patients not on regular follow up may result from them not taking their drugs as consistently as those who are regular attenders.

Clinicians who manage ulcerative colitis are aware that a proportion of their patients will develop cancer and many patients understand that they are at risk of developing colonic cancer. There is therefore considerable pressure on the clinician to 'do something'. How then should this difficult problem be managed?

Until newer[41] and more effective surveillance techniques are available the following policy seems reasonable. Most studies show that regular clinical follow up is important. Patients who have had ulcerative colitis should not be discharged but should have regular (if infrequent) appointments and be encouraged to return to hospital between appointments with the onset of any new colonic symptoms. At 8–10 years after their first attack, total colonoscopy should be performed with multiple biopsy specimens to find out if at any stage the patient has had an attack of total or extensive (beyond the splenic flexure) colitis. Those with left sided colitis should be reassured that their risk of cancer is little more than that of the normal population. Those with total or extensive colitis should be counselled and told that there is a risk, which will increase with the years, but that the risk is much less than was previously thought. They should be carefully followed up clinically and sigmoidoscopically and be examined colonoscopically as and when new symptoms arise.

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1 Langholz E, Munkholm P, Davidsen M, Binder V. Colorectal cancer risk and mortality in patients with ulcerative colitis. *Gastroenterology* 1992; **103:** 1444–51.
2 Sackett DL, Whelan G. Cancer risk in ulcerative colitis: scientific requirements for the study of prognosis. *Gastroenterology* 1980; **78:** 1632–5.
3 Greenstein AJ, Sachar DB, Smith H, Pucillo A, Papatestas AE, Kreel I, *et al.* Cancer in universal and left-sided ulcerative colitis: factors determining risk. *Gastroenterology* 1979; **77:** 290–4.
4 Edwards FC, Truelove SC. Course and prognosis of ulcerative colitis. Part IV. Carcinoma of the colon. *Gut* 1964; **5:** 15–22.
5 de Dombal FT, Watts JMcK, Watkinson G, Goligher JC. Local complications of ulcerative colitis: stricture, pseudopolyposis and carcinoma of the colon and rectum. *BMJ* 1966; **1:** 1442–7.
6 Devroede GJ, Taylor WF, Sauer WG, Jackman RJ, Stickler GB. Cancer risk and life expectancy of children with ulcerative colitis. *N Engl J Med* 1971; **285:** 17–21.
7 Kewenter J, Ahlman H, Hulten L. Cancer risk in ulcerative colitis. *Ann Surg* 1978; **15:** 824–8.
8 Gyde SN, Prior P, Allan RN, Stevens A, Jewell DP, Truelove SC, *et al.* Colorectal cancer in ulcerative colitis: a cohort study of primary referrals from three centres. *Gut* 1988; **29:** 206–17.
9 Henricksen C, Kreiner S, Binder V. Longterm prognosis in ulcerative colitis – based on results form a regional patient group from the county of Copenhagen. *Gut* 1985; **26:** 158–63.
10 Devroede G, Taylor WF. On calculating cancer risk and survival of ulcerative colitis patients with the life table method. *Gastroenterology* 1976; **71:** 505–9.
11 Lennard-Jones JE. Cancer risk in ulcerative colitis: surveillance or surgery. *Br J Surg* 1985; **72:** 884–6.
12 Dawson IMP, Pryse-Davies J. The development of carcinoma of the large intestine in ulcerative colitis. *Br J Surg* 1959; **47:** 113–28.
13 Morson BC, Pan LSC. Rectal biopsy as an aid to cancer control in ulcerative colitis. *Gut* 1967; **8:** 423–34.
14 Myrvold HE, Kock NG, Ahren CHR. Rectal biopsy and precancer in ulcerative colitis. *Gut* 1974; **15:** 301–4.
15 Ransohoff DF. Colon cancer in ulcerative colitis. *Gastroenterology* 1988; **94:** 1089–91.

16 Axon ATR. Carcinogenesis in ulcerative colitis: is surveillance worthwhile? *Can J Gastroenterol* 1990; **4:** 397–9.
17 Thurlby RG, Lennard-Jones JE. Colonoscopic surveillance for cancer in patients with chronic ulcerative colitis: is it working? *Gastroenterology* 1991; **100:** 570–2.
18 Collins RH, Feldman M, Fordtran JS. Colon cancer, dysplasia, and surveillance in patients with ulcerative colitis. *N Engl J Med* 1987; **316:** 1654–8.
19 Gyde S. Screening for colorectal cancer in ulcerative colitis: dubious benefits and high costs. *Gut* 1990; **31:** 1089–97.
20 Lynch DAF, Lobo AJ, Sobala GM, Dixon MF, Axon ATR. Failure of colonoscopic surveillance in ulcerative colitis. *Gut* 1993; **34:** 1075–80.
21 Jones HW, Grogono J, Hoare AM. Surveillance in ulcerative colitis: burdens and benefit. *Gut* 1988; **29:** 325–31.
22 Lashner BA, Silverstein MD, Hanaver SB. Hazard rates for dysplasia and cancer in ulcerative colitis. *Dig Dis Sci* 1989; **34:** 1536–41.
23 Lennard-Jones JE, Melville DM, Morson BC, Ritchie JK, Williams CB. Precancer and cancer in extensive ulcerative colitis: findings among 401 patients over 22 years. *Gut* 1990; **31:** 800_6.
24 Blackstone MO, Riddell RH, Rogers BHG, Levin B. Dysplasia-associated lesion or mass (DALM) detected by colonoscopy in longstanding ulcerative colitis: an indication for colectomy. *Gastroenterology* 1981; **80:** 366–74.
25 Lofberg R, Brostrom O, Karlen, Tribukait B, Ost A. Colonoscopic surveillance in longstanding total ulcerative colitis – a 15 year follow-up study. *Gastroenterology* 1990; **99:** 1021–31.
26 Woolrich AJ, DaSilva MD, Korelitz BI. Surveillance in the routine management of ulcerative colitis: the predictive value of low-grade dysplasia. *Gastroenterology* 1992; **103:** 431–8.
27 Leidenius M, Killokumpu I, Husa A, Riitula M, Sipponen P. Dysplasia and carcinoma in longstanding ulcerative colitis: an endoscopic and histological surveillance programme. *Gut* 1991; **32:** 1521–5.
28 Rutegard J, Ahsgren L, Stenling R, Janunger KG. Ulcerative colitis. Cancer surveillance in an unselected population. *Scand J Gastroenterol* 1988; **23:** 139–45.
29 Rosenstock E, Farmer RG, Petras R, Sivak MV, Rankin GB, Sullivan BH. Surveillance for colonic carcinoma in ulcerative colitis. *Gastroenterology* 1985; **89:** 1342–6.
30 Fuson JA, Farmer RG, Hawk WA, Sullivan BH. Endoscopic surveillance for cancer in chronic ulcerative colitis. *Am J Gastroenterol* 1980; **73:** 120–6.
31 Nugent FW, Haggitt RC, Gilpin PA. Cancer surveillance in ulcerative colitis. *Gastroenterology* 1991; **100:** 1241–8.
32 Rex DK, Lehman GH, Ulbright TM, Smith JJ. Screen colonoscopy in asymptomatic average – risk persons with negative occult blood tests. *Gastroenterology* 1991; **100:** 64–7.
33 Hardcastle JD, Chamberlain J, Sheffield J, Balfour TW, Armitage NC, Thomas WM, *et al.* Randomised, controlled trial of faecal occult blood screening for colorectal cancer. *Lancet* 1989; i: 1160–4.
34 Fozard JBJ, Dixon MF. Colonoscopic surveillance in ulceration colitis – dysplasia through the looking glass. *Gut* 1989; **30:** 285–92.
35 Dixon MF, Brown LJR, Gilmour HM, *et al.* Observer variation in the assessment of dysplasia in ulcerative colitis. *Histopathology* 1988; **13:** 385–97.
36 Melville DM, Jass JR, Shepherd NA, *et al.* Dysplasia and deoxyribonucleic acid aneuploidy in the assessment of precancerous changes in chronic ulcerative colitis. Observer variation and correlations. *Gastroenterology* 1988; **95:** 668–75.
37 Brostrom O, Lofberg R, Ost A, Reichard H. CAncer surveillance of patients with longstanding ulcerative colitis: a clinical, endoscopical, and histological study. *Gut* 1986; **27:** 1408–13.
38 Lennard-Jones JE, Ritchie JK, Morson BC, Williams CB. Cancer surveillance in ulcerative colitis: experience over 15 years. *Lancet* 1983; ii: 149–52.
39 Manning AP, Bulgim OR, Dixon MF, Axon ATR. Screening by colonoscopy for colonic epithelial dysplasia in inflammatory bowel disease. *Gut* 1987; **28:** 1489–94.
40 Riddell RH, Goldman H, Ransohoff DF, Appelman HD, Fenoglio CM, Haggitt RC, *et al.* Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. *Hum Pathol* 1983; **14:** 931–68.
41 Rubin CE, Haggitt RC, Burmer GC, Brentnall TA, Stevens, AC Levine DS, *et al.* DNA aneuploidy in colonic biopsies predicts future development of dysplasia in ulcerative colitis. *Gastroenterology* 1992; **103:** 1611–20.