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Colonic Cancer Surveillance in Ulcerative Colitis is Not Essential for Every Patient

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It is generally recognised that there is an increased risk of colonic cancer in patients with long-standing extensive colitis, and regular annual or biennial colonoscopic surveillance protocols have been recommended in order to detect early cancer. There is, however, little evidence to suggest that these protocols are of value. There have been no properly conducted controlled trials in this area, and the studies that have been reported are flawed by selection bias, the inclusion of patients with "pseudo disease" and protocol violators. Many studies have not distinguished between "screening colonoscopy" and "colonoscopic surveillance". Some have not drawn attention to the failures in the surveillance, i.e. patients with Dukes' grade C or worse, and overall the conclusions drawn have been unrealistically optimistic. The diagnosis of low grade dysplasia which has been accorded importance is insensitive, non-specific and is subject to gross interobserver error. It is of little clinical value. Colonoscopic surveillance using currently available techniques is of only marginal benefit to patients included within the protocol. It is not cost-effective and cannot be made to be so.

Key words: ulcerative colitis, dysplasia, cancer surveillance, colonic cancer, colonoscopic surveillance
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INTRODUCTION

COMPELLING evidence accumulated over many years indicates that ulcerative colitis is a premalignant condition. The major risk of cancer is in individuals who have extensive ulcerative colitis (proximal to the splenic flexure), and in whom the condition has been present for more than 10 years. The danger of malignant change increases with time. The precise relative risk of malignancy for a colitic compared with the normal population in earlier studies was exaggerated because figures were flawed by selection bias, most studies being reported by tertiary referral centres. Population-based studies provide more realistic estimates, the increased risk over the normal population varying from 0 [1] to 8 [2].

Gastroenterologists and many patients with ulcerative colitis are aware of the increased risk of cancer, and there is pressure to take steps to minimise it. The only completely effective method of prevention is proctocolectomy, an option previously advocated particularly at a time when the risk of cancer was thought to be higher than it is today. Total colectomy with the fashioning of an ileal pouch and ileo–anal anastomosis today offers patients a more acceptable alternative to ileostomy, but most patients are not prepared to undergo this procedure without good reason, and a majority of gastroenterologists do not consider the risk of cancer to be high enough to warrant this approach for cancer prophylaxis alone. An alternative way to reduce the risk of cancer death is the adoption of some form of surveillance to identify cancer at a curative stage.

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THE SURVEILLANCE THEORY

The observation that dysplastic change within the rectal mucosa might act as a marker for colonic cancer elsewhere in ulcerative colitis [3] was hailed as a breakthrough because it suggested that regular sigmoidoscopy with biopsy might identify those particularly at risk of developing colonic cancer. It quickly became apparent that most patients with cancer-associated colitis do not have rectal dysplasia, but with the advent of colonoscopy and the ability to biopsy more widely this became the preferred option. For the past 20 years, total colonoscopy on an annual basis has been regarded by many gastroenterologists as the most appropriate way of providing surveillance for colitics. In most surveillance protocols, patients with extensive disease and who have had colitis for longer than 8 years have been encouraged to undergo annual or biennial colonoscopy with multiple biopsies. Those shown to have persistent high grade dysplasia, a dysplasia-associated lesion or mass (DALM) or cancer have usually been advised to undergo colectomy. Those with low grade dysplasia have been followed more avidly by colonoscopy while those with normal histology have continued with normal surveillance.

ASSESSMENT OF SURVEILLANCE PROTOCOLS

It might be thought that this approach would have led to a reduction in mortality from colorectal cancer in patients with ulcerative colitis. Unfortunately, however, no large controlled studies have been undertaken, and the evidence that this approach is of benefit rests on uncontrolled (virtually anecdotal) reports, written by surveillance enthusiasts, and reviewed by others "in the field", some of whom may lack the objectivity normally applied to the review of scientific papers. When these publications are analysed in a more critical light, it is apparent that some are seriously flawed and others misleading [4–7].

In practice, most surveillance programmes identify only a small proportion of the colitis-associated cancers discovered at the referral centres. Many are detected at an advanced stage [8]. The identification of low grade dysplasia, on which much emphasis has been placed, is of limited value. It may be more cost-effective to screen the normal population than to undertake surveillance protocols designed as suggested above [4, 7, 9]. Attempts to improve the pick-up rate of cancer by increasing the frequency of colonoscopy or recruiting more patients makes the exercise even less cost-effective. In this paper, the above criticisms relating to colonoscopic surveillance will be considered in the light of published literature.

BY WHAT PARAMETERS SHOULD SURVEILLANCE STUDIES BE JUDGED?

When assessing a surveillance study, many factors have to be considered, but the most important is whether or not it will lead to a reduction in mortality. The only way to answer this question is to set up a randomly controlled study based not on the rate of cancer detection, but on the final outcome, i.e. mortality. If this is not done, a number of biases occur. The first is selection bias. A recent paper described an analysis of the mortality of patients attending a clinic retrospectively, dividing them into those who had accepted colonoscopic surveillance and those who had not [10]. Not surprisingly, it showed that cancers were detected earlier in those who accepted surveillance than in those who presented with symptoms of cancer or had refused surveillance. They drew the conclusion that these data indicated that surveillance was beneficial. As the accompanying editorial pointed out [11], the comparison was invalid because those who accepted surveillance were differently selected from those who did not. The second problem is what is known as pseudo disease bias. If success is rated as the discovery of an early cancer or dysplasia as opposed to a lower mortality, those cancers that are indolent and would not eventually have caused death are counted as successes for surveillance. This bias particularly applies to patients who are elderly, and who might have died from other causes first, and to others who have significant symptoms from their colitis that would have led to colectomy before the cancer became advanced. A third problem which is found in comparative studies is length bias, which affects all controlled cancer surveillance studies. However, as there have been no properly controlled clinical studies in colitis surveillance, this does not need to be considered in this article.

WHAT CONSTITUTES "SUCCESS" IN SURVEILLANCE?

Where proper controlled studies are not available for evaluation, the onus of proof of success must be laid upon those who advocate surveillance. The question at issue is whether or not colonoscopic surveillance is effective. For it to be effective, studies should show that the implementation of a protocol has led to the detection of a significant number of early cancers, and has made an impact on the management of colitis-associated cancers in the particular centre where it has been adopted. A secondary consideration is whether or not it is cost-effective.

In order to assess the published results, it is necessary to define what is meant by "success". In this analysis, success has been defined as the discovery of a cancer of Dukes' grade A or B as a result of a colonoscopy undertaken in a patient who had extensive (beyond the splenic flexure) ulcerative colitis for longer than 8 years and for the purpose of "surveillance" (as opposed to "screening"). The distinction between surveillance and screening is an important one. Many patients are referred to tertiary referral centres for the first time many years after the onset of colitis, during which time they may or may not have been properly investigated. It is normal practice in most centres on taking over the care of a new patient to perform a routine screening colonoscopy. This is not in any sense part of a "surveillance" protocol. Surveillance implies the ongoing, regular colonoscopic examination of patients who have just reached surveillance "age", i.e. 8 or 10 years after their first attack, or who are already enrolled in a surveillance protocol with at least one previous negative "screening" colonoscopy. Furthermore, the colonoscopy must have been undertaken for the purpose of surveillance not for new symptoms or prior to a planned operation for "disability". Those patients with cancer who cannot be counted as successes, therefore, are those in whom cancer is found at first colonoscopy undertaken late in the evolution of their disease, those with Dukes' C or worse, those who die, and patients whose cancer is detected by means other than colonoscopy. These observations may appear obvious, however, a recent paper purporting to demonstrate the potential predictive value of low grade dysplasia stated "surveillance . . . has led to the recognition of neoplasm in 10% including carcinoma in seven (6%) of 121" [12]. In fact, of the 7 patients with cancer, 3 died from metastases (one of which was only diagnosed in the operative specimen), 2 other patients recruited for the study had only left-sided colitis (and would have been ineligible for most surveillance protocols).

AN ANALYSIS OF 12 SURVEILLANCE STUDIES CARRIED OUT UP UNTIL 1992

12 well documented surveillance studies were undertaken before 1992 [8, 12, 13–22]. These have been analysed using the parameters of success set out in the previous paragraph. Table 1 shows that, in all, 92 cancers were found in 1916 patients. Most, but not all, of these cancers were found within the actual groups undergoing surveillance, but the figures analysed here include all the cancers reported in the 12 papers. Of the 92 cancers found, 40 were Dukes' C or more advanced. Eleven were discovered at operation or at autopsy, 17 were identified not by colonoscopy, but by either barium enema or sigmoidoscopy. Two were discovered at operation for low grade dysplasia (a condition few consider to be an appropriate sole indication for operation), Three fell outside the criteria laid down for surveillance in this analysis and in 8 cases the colonoscopy was the first one that had been done on the patient at least 13 years after onset of ulcerative colitis, and represented screening rather than surveillance. In all, only 11 of 92 cases (12%) could be counted as success for "surveillance" according to the criteria discussed previously.

Table 1. 12 *surveillance studies using* 1916 *patients*

Total cancer cases	92
Dukes' C (or more advanced)	40
Found at operation or autopsy	11
Found by sigmoidoscopy or barium enema	17
Operation undertaken for low grade dysplasia	2
Discovered outside protocol laid down in this analysis	3
Found at "screening" as opposed to "surveillance" colonoscopy	8
Total	81
Surveillance "success"	11 (12%)

Since the above analysis was carried out, further data have been published by one of the more successful tertiary referral centres which have followed a surveillance protocol since around 1974 [10]. They retrospectively analysed 2050 patients who had attended their clinic with colitis, and found 41 of them to have developed cancer. Only 19 had been in the surveillance group. Of these, 4 had died of cancer, one further patient had a Dukes' C cancer, 2 had left-sided disease only, in 3 the cancer was missed at colonoscopy and found at operation performed for disease control, 2 had defaulted and presented again with new symptoms and were then diagnosed. One appears to have had a screening colonoscopy done for the first time at 18 years following the onset of disease. Overall, it seems that only 7 of the 41 (17%) patients with cancer benefited from surveillance.

In practice, however, the number is less than this because not all cancer in ulcerative colitis is lethal. The 5 year survival after diagnosis in unselected patients with cancer-associated ulcerative colitis is between 34 and 62% [23, 24]. Less than 10% of the cancer patients in that particular centre of excellence were helped by the service.

THE MYTH OF LOW GRADE DYSPLASIA

Few histological discoveries have turned out to be as disappointing as dysplasia in ulcerative colitis. It seems eminently logical to assume that cancers will develop in colons that show a field change of "pre-cancer". The diagnosis of pre-cancer in ulcerative colitis, however, is bedevilled by the lack of sensitivity, specificity and reproducibility of dysplastic change. Whereas most pathologists are able to distinguish high grade dysplasia from normality, it is the gradations between them that cause problems, and this is made more difficult in ulcerative colitis where the background mucosa is often inflamed and exhibits reactive changes that can be misleading. Even expert gastrointestinal pathologists disagree as to the presence or absence of dysplasia when tested "blindly" [25, 26]. The insensitivity of the diagnosis is apparent when one considers that around 30% of ulcerative colitis-associated cancers occur in a colon where there is no dysplasia in the rest of the bowel. Conversely, its specificity is poor in that the majority of patients who have dysplasia do not have cancer [27–29].

Most large colonoscopic surveillance studies have recorded the numbers of patients with low grade and high grade dysplasia. When these are analysed, it becomes apparent that the presence of low grade dysplasia is not a good predictor of cancer the first time low grade dysplasia is identified. In an analysis of ten studies comprising 1603 patients, 276 were reported at some stage to have low grade dysplasia (17%). The total number of cancers found in the whole group was 72 (4.5%), whilst the number of cancers found in those at their initial diagnosis of low grade dysplasia was 25 (9.0%). If DALMs are excluded on the grounds that biopsies in these may have been taken from a superficial part of the cancer itself, the percentage of cancers found in this group falls to 6.5%. The finding of low grade dysplasia without a mass lesion seems, therefore, to have little immediate value in assessing the colon.

Bernstein and associates [30] performed a similar analysis on a subset of these data. 1225 patients satisfied their inclusion criteria. Of these (excluding DALMS), 69 patients had low grade dysplasia on initial colonoscopy and cancer was found in 3 (4.3%). In all, 210 patients developed low grade dysplasia at some time during surveillance and, of these, 17 developed cancer (8.1%). However, 9 of 95 patients (9.5%) with "indefinite" dysplasia also developed cancer, so it is difficult to understand why these authors have stated "immediate colectomy is essential for all patients . . . with low grade dysplasia" especially when they quote a figure of 7% risk of cancer overall in ulcerative colitis after 20 years of disease (little different from their low grade dysplasia risk).

One possible way to improve the value of low grade dysplasia might be to adopt more stringent criteria for its diagnosis. The St. Mark's group has recently re-analysed their data along these lines [31]. Excluding DALMs, they accepted only 9 patients as having low grade dysplasia out of the 51 previously diagnosed, and in so doing improved the specificity of low grade dysplasia as a marker for malignancy. However, in regrading low grade dysplasia of the 47 biopsies diagnosed as low grade dysplasia by one or other, they agreed in less than half (20/47). This serious interobserver variation indicates that low grade dysplasia is not a pathological diagnosis on which important management decisions can be made.

In summary, high grade dysplasia and DALMs are important in the management of ulcerative colitis, but may represent superficial biopsies taken from colonic cancers. In contrast, the presence of low grade dysplasia is subject not only to interpretation bias, but is neither a sensitive nor specific marker of cancer at the time of its diagnosis.

COST-EFFECTIVENESS

The costs involved in undertaking regular colonoscopy are considerable, not only in financial terms, but in the inconvenience, discomfort and, for some, the loss of dignity entailed in regular examinations of this nature. There is also a small morbidity associated with the procedure. A few early cancers have been identified by surveillance protocols, but they are a minority. The argument against colonoscopic screening, however, is not that it is totally ineffective, but that it is a poor use of resources. In 11 of the 12 studies quoted earlier, the number of colonoscopic examinations undertaken were recorded. 3807 colonoscopies in all were performed to detect 8 early cancers (as defined on the criteria set out previously). This gives a return of one early cancer per 476 examinations. Surveillance of the normal population between the ages of 50 and 80 on a 5 yearly basis is likely to do better than this [4, 7, 9], to say nothing of the follow-up of patients found positive on occult blood testing.

Those who hold strong positive beliefs about surveillance studies may argue that the solution to the effectiveness side of the equation would be to follow up patients more avidly, chase defaulters and recruit more enthusiastically. Some authorities take the view that surveillance should include all patients who have inflammatory disease extending beyond the rectum, not just those with extensive colitis. There is little doubt that if these measures were applied, more cancers would be identified. However, in order to do so, the number of colonoscopies would have to rise disproportionally. In practice, this would mean that the cost side of the equation would rise even more, and the cost-effectiveness of surveillance would fall further. In most of the 11 studies quoted, the authors recommended annual or at least biennial colonoscopy, yet only 3807 colonoscopies were performed on 1603 patients, an average of under two colonoscopies per patient, even though the studies had in the main followed patients for 10 or more years. It follows that even enthusiasts have some difficulty in persuading their patients of the benefits of surveillance. Would more frequent colonoscopy have helped the success rate? In the recent paper by Choi and associates [10], of the 19 patients with colorectal carcinoma that had undergone cancer surveillance, a diagnosis was made after a median of only

2 years surveillance and a median of 2 colonoscopies. The data suggest that cancers are diagnosed relatively more frequently immediately after the patient has been enrolled in the study rather than later, and argues that long term regular surveillance is likely to become less cost-effective the longer it is pursued.

The data indicate that colonoscopic surveillance does not and cannot work.

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