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Leading article

Screening for colorectal cancer in ulcerative colitis: dubious benefits and high costs

The primary role of the medical profession is to diagnose and treat members of the population who identify themselves as being 'sick' in some way. In this situation 'patients' approach the doctors. It is only recently that doctors have involved themselves in 'screening' apparently healthy members of the population in order to diagnose disease at a presymptomatic stage, when it is presumed treatment will be more effective.

In this context of 'screening,' the contract between the doctor and the patient has an ethical element not present in ordinary clinical diagnosis and treatment. Elaborating on this point, Thomas McKeown, in the late 1960s, wrote:

> When a patient seeks medical advice the doctor's position, ethically, is relatively simple: he undertakes to do his best with the knowledge and resources available to him. He cannot be criticized when the state of medical knowledge does not enable him to treat effectively or even diagnose accurately the condition for which his advice is sought; nor can he undertake in all cases to assemble the full range of facilities for investigation and treatment from which his patients might conceivably benefit.
>
> The position is quite different in screening, when a doctor or public medical authority takes the initiative in investigating the possibility of illness or disability in persons who have not complained of signs or symptoms. There is then a presumptive undertaking, not merely that abnormality will be identified if it is present, but that those affected will derive benefit from subsequent treatment or care. This commitment is at least implicit, and except for research and the protection of public health, no one should be expected to submit to the inconvenience of investigation or the anxieties of case-finding without the prospect of medical benefit. The obligation exists even when the patient asks to be screened, for his request is then based on the belief that the procedure is of value, and if it is not it is for the medical people to make this known.[1]

It is not sufficient therefore to offer a screening procedure which it is supposed will benefit the patient; the screen must have been proved to benefit the patient. The two basic obligations of any screening procedure are: (i) to ensure that the screening procedure is effective; and that if it is (ii) it makes better use of limited resources than available alternatives.[1]

Screening for colorectal cancer in ulcerative colitis patients has become part of routine clinical care. The question which must be asked (and which should have been asked *before* the screening procedure became widely used) is whether it fulfils these two basic obligations.

The first obligation is to ensure that the procedure is effective. 'Effectiveness' in terms of a screening procedure for cancer should be measured in terms of increased survival in the group of patients screened.

The way to show whether a screening procedure increases survival is to randomise patients eligible for screening into two groups. The 'screened' group would undergo ordinary clinical care, plus the screening procedure, which in this instance would be colonoscopy and multiple biopsies for the detection of dysplasia. The non-screened group would undergo ordinary clinical care only (which would of course include standard investigations such as sigmoidoscopy and barium enema, when deemed necessary).

A life table would then be plotted of the survival in the two groups. The methodology is well described in papers concerning the large American randomised trial which showed conclusively that there was an increased survival in women undergoing screening for breast cancer.[2]

At present we have no idea whether screening for cancer in ulcerative colitis increases survival as the randomised trials necessary to show this were not set up before the screening procedure was widely introduced.

Judging by the volume of published reports, gastroenterologists and histopathologists have directed all their attention to the 'process' of the screening procedure. Many publications describe in detail the number of cancers detected, the Dukes's stage of cancers detected, cancers detected in relation to dysplasia, high grade, low grade, or indeterminate. Distinctions are being made in terms of the yield of cancers between 'screening' and ongoing 'surveillance' in an attempt to access the effectiveness of the screening procedure. The detail of the 'process' has been addressed without the necessary structures being set up to evaluate the 'outcome' of the process.

As far as the patients are concerned, it is irrelevant how many cancers screening detects, at what stage they are detected, or whether correlations between dysplasia and cancer are found unless the end result is that survival of patients undergoing screening is increased in relation to a similar unscreened group.

There are, however, good reasons for supposing that early detection of colorectal cancer might lead to increased survival. We know from large studies concerning survival of patients with colorectal cancer complicating ulcerative colitis that without screening the five year survival is poor (approximately 33% at five years, similar to the survival from colorectal cancer in the general population), and that survival is dependent upon the stage at which the cancer is diagnosed.[3–7]

If colorectal cancer is diagnosed at Dukes's stage A survival is usually in excess of 20 years; when diagnosis is

*Results of screening tests in relation to diagnostic tests**

	Diagnostic test	
Screening test	*Positive*	*Negative*
Positive	a	b
Negative	c	d

Sensitivity of the screen $= \frac{a}{a+c}$

Specificity of the screen $= \frac{d}{b+d}$

c = false negatives of the screening test (cancers/precancers missed by the screen)
b = false positives of the screening test (cancers/precancers wrongly diagnosed by the screen)

*Diagnostic test for colorectal cancer in ulcerative colitis is either definitive diagnosis made at operation or symptomatic diagnosis of late complications of cancer.

made at Dukes's stage B or beyond, survival tends to be poor.

It is a reasonable but unproved hypothesis that if colorectal cancer in ulcerative colitis could be diagnosed at a precancerous stage (dysplasia) or at an early stage (Dukes's A), survival would be increased.

Is the screening procedure presently used likely to be effective in detecting early cancer?

Screening procedures for cancer are never 100% accurate (Table). They will miss some cancers that are present (false negatives) and they will diagnose some cancers that are not present (false positives).

In screening for colorectal cancer in ulcerative colitis, on available evidence, it is likely that false negatives rather than false positives will be the major problem – that is, cancers will be missed. False positives – that is, patients wrongly diagnosed as having cancer/precancer – are difficult to identify with certainty. Colons may be removed which show repeated high grade dysplasia but it is uncertain, because the clinical course of dysplasia is not known, in what proportion of cases the dysplastic mucosa would continue to remain dysplastic and in what proportion the dysplastic lesions would have progressed to frankly invasive carcinoma. Among the patients undergoing colectomy for dysplasia will be an unknown number who would not have developed carcinoma. These are the false positivies of the screening.

The Table shows the usual format for expressing the validity of a screening procedure in terms of false positives and false negatives and also in terms of the sensitivity and specificity of the screen.

The sensitivity of a screening test is the number of true positives (compared with a verification or 'diagnostic' test) correctly identified by the screen. In terms of screening for cancer in ulcerative colitis, the sensitivity expresses the number of cancers/precancers detected by screening, as a proportion of all cancers eventually diagnosed.

The specifity of a screening test is the number of true negatives diagnosed by screening, expressed as a proportion of all negatives.

Problems with the use of 'dysplasia' as a marker in the screening test

False negatives, in this particular screen are likely, on a priori grounds, to be frequent, given factors widely known concerning dysplasia in relation to colon cancer in ulcerative colitis.

Many studies have shown that colorectal cancer in ulcerative colitis can arise de novo with no associated dysplastic lesions. These cancers will therefore be missed by the screening test (unless the biopsy specimen happens to be taken at the actual site of the cancer). Ransohoff *et al* showed that only 50% of colectomy specimens showed dysplasia distant from the cancerous lesion.[8]

It is known that dysplastic lesions in ulcerative colitis occur in a patchy distribution. Dysplastic areas may therefore be missed, even with multiple biopsies.

Multiple biopsies probably sample less than 1% of the colonic surface area present, and given that dysplasia is either not present in relation to a cancer, or present only surrounding the cancer, or present throughout the colon but in a patchy distribution, the probability of even multiple biopsies hitting the requisite area are relatively low. Repeatability is a problem since it is impossible to take biopsy specimens from the same mucosal site. Observer errors in histopathological diagnoses also contribute to false positive and false negative rates.[8-15]

Observer error when viewing slides is another source of error. Major discrepancy rates between separate expert histopathologists viewing the same slides vary from 4–7·5% with false positives being the main source of error.[16 17]

Apart from problems with the screening technique itself, cancers may be missed or misdiagnosed for other reasons. Cancers not present at an initial screening may develop in the interval between two screens ('interval cancers'). In screening for cancer in ulcerative colitis it would be difficult to be certain that a cancer occurring in the interval between the two screens was a 'true' interval cancer. Given the relative inefficiency of multiple biopsies for detecting cancer in the colon, cancers occurring in the interval between two screens would be more likely to be cancers missed at the previous screen (false negatives).

Low compliance rates will be another reason for cancers being missed.

For a screening test to be effective, the screening test must be acceptable to patients in order to obtain a high degree of compliance with screens.

In the report of a large prospective study carried out at St Mark's hospital, the authors stated that having set out with a group of 303 patients, 43 patients discontinued follow up, 20 of these refusing to attend. Two cancers were missed in those 20 refusing screening.[18]

In another recent study describing cancer surveillance in ulcerative colitis patients in a district health authority over a 10 year period, of 313 patients followed up, 84 patients were lost to follow up, five of whom were subsequently found to have developed cancer.[19]

Certainly the validity and repeatability of the screening test under consideration are a cause for concern. On the evidence so far we would not expect the screening procedure to be very effective.

In the absence of any randomised trials evidence concerning the effectiveness of the procedure in terms of survival must be based on the few prospective trials of surveillance reported in the literature. Although there are a considerable number of publications concerning retrospective data, selection biases in these studies make the data unsuitable for evaluating a screening procedure.

It is worth considering in detail three major prospective surveillance studies recently reported.[10 11 18]

Prospective study from St Mark's Hospital, London

A prospective trial has been running for over 15 years at St Mark's Hospital, London.[18] In the summary of their paper the authors state: 'Despite regular surveillance, carcinoma developed in 13 of the 186 extensive colitis patients with a history of disease for ten years or more. Of the total 16 carcinomas in these 13 patients, 11 were Dukes's Stage A, 3 Stage B, 1 Stage C and 1 was inoperable.' In this study, therefore, a high proportion of patients (11/16) were diagnosed at Dukes's stage A. Only three of these 13 patients,

however, seem to have been diagnosed as having cancer by the screening procedure on its own.

Quoting from the report: 'Surgery was undertaken in 10 patients who were in good health, solely because of severe dysplasia changes observed on biopsy (3 had carcinoma). The rest of the cancers were diagnosed either pre-operatively by barium enema or sigmoidoscopy or at operation performed for other reasons.' There is a problem with interpreting the results of this study in that in the early years of the study patients underwent regular follow up ('ordinary clinical care'), colonoscopy only being introduced in the study from 1974 onwards.

From the report it is clear that on the whole patients followed up in this study had their cancers diagnosed at an early stage. Early diagnosis, however, seems to have been achieved by high levels of follow up attained in the group under review, and by expert clinical care, rather than by the screening procedure itself.

Prospective study from Lahey Clinic Medical Center, USA

In the prospective study from the Lahey Clinic Medical Center,[20] during a 10 year period 151 patients with longstanding (>7 years) ulcerative colitis were enrolled, 104 with extensive colitis and 47 with left sided disease.

Screening identified 12 patients on initial biopsy with dysplasia (four high grade dysplasia, eight low grade dysplasia). At colectomy, three of the patients with high grade dysplasia had unsuspected carcinoma (one Dukes's B and two Dukes's C). Of the eight patients with low grade dysplasia, four developed high grade dysplasia on follow up, one of whom on colectomy had a carcinoma (Dukes's C) as did one of the low grade dysplasia patients (Dukes's B).

Therefore, in the 12 patients diagnosed as having high grade or low grade dysplasia, 11 underwent colectomy with the diagnosis of five cancers (two Dukes's B, three Dukes's C). In this study it seems that the screening procedure did in fact diagnose the cancers present, not otherwise suspected clinically, but that diagnosis was at a late stage where survival would be likely to be poor.

Prospective study from Leeds Royal Infirmary

In a prospective study reported by Manning *et al*[21] from Leeds Royal Infirmary, 112 extensive colitis patients with longstanding disease (>8 years' duration) were screened. Of these 112 patients, two patients were suspected of having carcinoma from barium enema examination; subsequent colonoscopy showed high grade dysplasia, and carcinoma (Dukes's stage not stated) was diagnosed at subsequent colectomy.

Another 10 underwent colectomy without carcinoma being diagnosed, leaving a continuing surveillance group of 100 patients. High grade dysplasia was diagnosed at a subsequent follow up on one of these patients and at colectomy a Dukes's A carcinoma was found.

The screening procedure in this study therefore diagnosed one early cancer after 354 colonoscopy examinations, the other two cancers diagnosed being suspected from barium enema examination before colonoscopy was carried out.

Discussion

It is difficult to compare the results in these three prospective studies as the entry criteria for the patients under review, and techniques used in the screen, were not identical. All studies found a heavy workload in carrying out the continuing surveillance of colonoscopy and multiple biopsies.

In the two English studies, out of 19 cancers diagnosed, only three seem to have been diagnosed by screening itself. In the American study the six cancers diagnosed were all detected by screening but only one of these was detected at a stage (Dukes's A) where survival might be expected to be improved.

Only a randomised controlled trial could establish whether patients diagnosed with cancer in the groups screened survive longer than those with cancer diagnosed in the control group undergoing routine clinical care. With screening for cancer in ulcerative colitis being so widely practised and available, it might be difficult to set up such a trial. It would require large numbers of patients to be recruited and followed up for long time periods (around 15–20 years) to obtain meaningful results. Given the rarity of ulcerative colitis as a disease, and the even smaller numbers of patients in the 'high risk' extensive colitis group, a multicentre trial would need to be funded to recruit sufficient numbers of high risk patients to give significant results over a reasonable time period.

The evidence available from continuing prospective trials suggests that at present the 'costs' of screening probably outweigh the 'benefits.' It is by no means clear from available evidence that the screened group would be likely to survive longer than the group undergoing 'ordinary clinical care.' As 'ordinary clinical care' in the English prospective studies diagnosed 80% of the cancers eventually found, are we justified in continuing surveillance in its present form? We must consider the cost to the patients in terms of travelling costs, time lost from work, and undergoing a relatively unpleasant and occasionally harmful procedure which is possibly of limited benefit in terms of survival.

In a recently reported study of surveillance in a district health authority costs were estimated for each cancer detected as £6015/cancer detected.[19] If the patient derives no benefit in terms of survival, however, detecting a cancer is not very helpful, whether the monetary cost is high or low. What we really need to cost is the cost per life year prolonged or cost per life saved.

The most positive step forward would be to find a very efficient marker of cancer/precancer in the colons of high risk patients and jettison the whole procedure of colonoscopy and multiple biopsies as of limited value. Alternative markers for cancer have been investigated, such as the quality of the mucus adjacent to cancer, abnormal staining patterns, changes in nuclear material, and immunohistological markers, but at present these do not offer an effective prospect.

In this era of health care, where there are cash limits, with great pressure to use resources efficiently, when every expenditure is seen as an 'opportunity cost,' in that the money spent in one area is not free to be spent in another, we have to ask ourselves again whether screening for colorectal cancer in ulcerative colitis fulfils the two basic criteria for a screening procedure: (i) Is the screen effective? We have to say we don't know. (ii) If it is, does it make better use of limited resources than available alternatives? While the first question remains unanswered, we cannot answer the second.

The way forward must be a randomised controlled trial, or an alternative 'marker' to be used in screening. One thing is certain, we should not go on as we are.

SYLVIA GYDE

Department of Public Health Medicine,
Highcroft Hospital,
Erdington, Birmingham B23 6AX

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