Pergamon

European Journal of Cancer Vol. 31A, Nos. 7/8, pp. 1178–1182, 1995

0959-8049/95 $9.50+0.00

0959-8049(95)00132-8

Is Colonoscopic Cancer Surveillance in Ulcerative Colitis Essential for Every Patient?

J.E. Lennard-Jones

Surveillance aims to diagnose precancer or cancer at a surgically curable stage. Cancer complicating ulcerative colitis affects only 1–2 per million of the general population annually. The risk is low within 10 years of disease onset, and in proctitis or left-sided colitis. It is approximately one in 120 per year for those with extensive disease after 10 years from onset. Results of surveillance programmes from regional hospitals among 423 patients led to surgery for precancer or cancer once every 123 colonoscopies; there were no cancer deaths during surveillance and all 4 cancers were Dukes' stage A or B. At referral centres, many patients have dysplasia at the first colonoscopy. Two-thirds of cancers in colitis develop in the recto-sigmoid; flexible sigmoidoscopy has a role in surveillance which is untested. Colonoscopic surveillance is not appropriate for most patients with colitis; it is worthwhile but not essential for those with long-standing extensive disease.

Key words: ulcerative colitis, cancer surveillance, dysplasia, colonoscopy
Eur J Cancer, Vol. 31A, Nos 7/8, pp. 1178–1182, 1995

THE PROPOSITION

CANCER SURVEILLANCE can be defined as a regular programme of investigation, independent of the presence or absence of symptoms, with the aim of detecting precancer or cancer at an early curable stage. Is it essential for every patient with ulcerative colitis and should it involve colonoscopy?

Surveillance can be justified only if there is a reasonable expectation of finding an abnormality, otherwise much work is undertaken at considerable cost, with little benefit. Evidence for precancer must be sensitive enough to give confidence in its detection and specific enough to warrant colectomy. Detection of cancer should be possible before the tumour involves lymph nodes or causes distant metastases because at this stage (Dukes' stage A or B) the surgical cure rate is at least 80% [1, 2]. The risk of investigation should be minimal. The cost to the patient in terms of time and discomfort, and to the community in use of health resources should both be acceptable. If every patient is to be helped, recruitment should be complete, and patients should comply both with the investigations and advice to accept surgical treatment when it is given. If all these conditions are fulfilled, a surveillance programme can be described as essential; if they are not, it is either unjustified or optional.

EXPECTATION OF FINDING AN ABNORMALITY

Cancer complicating colitis is uncommon. Three series based on records from regional hospitals (Table 1) in Israel and Sweden over periods of 10–34 years detected 142 such colorectal cancers in large populations of 1.3–1.5 million, an average annual incidence of 1.7 per million of the general population [3–5]. A population based surveillance programme for cancer complicating colitis is thus inappropriate.

Correspondence to J.E. Lennard-Jones at 55 The Pryors, East Heath Road, London NW3 1BP, U.K.

Among sufferers with ulcerative colitis, it is important to distinguish between relative risk and absolute risk. The relative risk may be high because the risk in the general population is low, as occurs among young healthy persons. Absolute risk for all patients with colitis has been assessed in a large Swedish series [4] as one cancer per 391 patient years of follow-up. Within the colitic population (Table 2), absolute risk varied with the extent and duration of the disease, but not the age of the patient at onset [4]. For a patient with proctitis, the risk was 1 in 1241, for those with left-sided colitis 1 in 657, and for patients with total colitis it was 1 in 204 per patient year of follow-up. In our own series of patients (Table 3), with disease involving most or all of the colon, the risk was zero during the first decade after onset of symptoms, one cancer in 137 patient years during the second decade and one in 103 patient years thereafter [6].

A surveillance programme is thus inappropriate for every patient with colitis. A reasonable expectation of abnormal findings is likely in patients with extensive colitis once 10 years have elapsed since onset.

ARE THERE OTHER HIGH RISK GROUPS?

Patients in whom the rectum is retained after colectomy have a risk of carcinoma comparable to those with extensive colitis. Clearly, they need sigmoidoscopy, not colonoscopy.

Evidence is accumulating that patients with the combination of pericholangitis or sclerosing cholangitis and colitis are at high risk of carcinoma and for them colonoscopy is necessary [7, 8].

IS DYSPLASIA AS A MARKER SUFFICIENTLY SENSITIVE TO BE USEFUL?

Approximately a quarter of cancers complicating colitis are not associated with detectable dysplasia at a distance from the tumour [2, 9, 10]. Dysplasia is patchy, and it has been estimated that 33 biopsies from the whole colon are needed to give a 95% chance of detection when it is present [11]. If elevated lesions

Table 1. Cancer incidence in three defined geographical areas

Ref	Country	Period	Population	Patients	Cancer	Annual incidence (per million)
[3]	Sweden	1945–1979	1 520 000	1339	25	0.48
[4]	Sweden	1958–1984	1 300 000	3117	91	2.7
[5]	Israel	1970–1980	1 300 000	1035	26	2.0

The mean incidence was 1.73 per million population annually.

Table 2. Cancer risk among all sufferers from colitis showing that the risk varies with extent of disease

	Cancer	Patient years	Risk per year
Proctitis	9	11 170	1 in 1241
Left-sided	17	11 169	1 in 657
Pan-colitis	65	13 241	1 in 204

Data from [4].

Table 3. Cancer risk among a series of patients with extensive colitis showing that the risk is small during the first decade but is clinically significant thereafter [6]

Duration (years)	Cancer	Patient years	Risk per year
0–9	0	1406	0
10–20	11	1512	1 in 137
20+	11	1130	1 in 103

are present, targeted biopsies are likely to increase the sensitivity of each biopsy [12, 13]. Thus, dysplasia, if present, can usually be detected if care is taken. As discussed below, the presence of dysplasia is clinically significant but its absence does not guarantee freedom from carcinoma at the time of biopsy or later.

IS DYSPLASIA AS A MARKER OF PRECANCER OR CANCER SUFFICIENTLY SPECIFIC TO BE USEFUL?

Currently, the diagnosis of precancerous change in the epithelium depends on the recognition of dysplasia. When high grade dysplasia is found or dysplasia on the surface of a broad-based or villous lesion, the likelihood of synchronous carcinoma is approximately 40% [14]. The specificity of high grade dysplasia or a dysplastic mass lesion for predicting future development of carcinoma is unknown, but is likely to be high.

The specificity of low grade dysplasia is controversial. Lesser degrees of dysplasia are difficult to distinguish histologically from regenerative changes as a result of inflammation. Minor histological changes are subject to high interobserver variation. If dysplasia is only diagnosed when it is unequivocal using agreed criteria, specificity improves. Thus, in our series, when low grade dysplasia was reported during the period 1965–1987, the cumulative likelihood of high grade dysplasia or cancer was 16% during the next 5 years [6]. Re-examination of the biopsies by current criteria led to acceptance as dysplastic of only 27 of 107 biopsies previously reported as showing low grade dysplasia. Using these current criteria, the specificity of low grade dysplasia would have improved so that approximately half the patients developed high grade dysplasia or carcinoma within the next 5 years [15].

A detailed pathological study, in which 32 endoscopic type biopsies were taken from each of 100 colectomy specimens, suggests that when high or low grade dysplasia is found, there is a 9-fold greater likelihood of synchronous carcinoma than when it is absent [10]. In addition, the likelihood of high grade dysplasia or carcinoma in the next 5 years is at least 50%. Unequivocal dysplasia, when it is present, is thus a reasonably specific marker both of synchronous and future carcinoma, and warrants colectomy.

ARE OTHER TECHNIQUES OR MARKERS OF PRECANCER LIKELY TO BECOME AVAILABLE?

Mucosal brushings sample a wider area of mucosa than biopsies and yield a sample composed mainly of epithelial cells, the characteristics of which can be clearly defined [16]. This technique requires further study.

Aneuploidy appears often to precede dysplasia [11, 17], and when present aids in its definition. Genetic markers are in the course of development for example, the immunohistochemical detection of p53 protein overexpression, and there are likely to be markers of precancer and to aid in the definition of dysplasia [18].

CAN CANCER BE DETECTED AT A SURGICALLY CURABLE STAGE?

Cancer tends to be associated with either a proliferative lesion, an atypical ulcer or stricture [13]. Endoscopy can thus often detect cancer even if dysplasia or other markers of precancer are absent elsewhere in the colon.

IS THERE A RISK IN COLONOSCOPY?

No complication has been recorded as a consequence of over 3000 colonoscopies performed during cancer surveillance programmes in colitis.

DO PUBLISHED RESULTS FROM REGIONAL HOSPITALS BEAR OUT PREDICTIONS?

Four series [19–22] conducted over 12–15 years (Table 4) in regional hospitals among 423 patients, mostly with extensive colitis, have resulted in 11 operations for dysplasia and the diagnosis of four cancers, all Dukes' stage A or B. One patient died of cancer before entering the programme [21] and another after leaving it [22]. There was no cancer death during surveillance.

These recent results fulfil the predicted frequency of finding a clinically significant lesion approximately once every 120 patient years of follow-up because an abnormality leading to colectomy was observed in 15 of 1844 colonoscopies (one in 123). Since all

Table 4. Results of cancer surveillance at four regional hospitals

Ref.	Country	Years	Patients	Colonoscopies	Operation dysplasia	Cancer	Death
[19]	Sweden	1973–1988	72	291	9	AA	
[20]	Finland	1976–1989	66	182	–	–	
[21]	Sweden	1977–1991	131	632	2	B	1*
[22]	England	1978–1990	154	739	0	A	1*
	Total		423	1844	11	4	

* One death before starting and one after leaving surveillance.

cancers were surgically curable and there were no cancer deaths, the results can be regarded as excellent, despite the fact that one of these series was published under the title "Failure of colonoscopic surveillance in ulcerative colitis" [22].

DO PUBLISHED RESULTS FROM TERTIARY REFERRAL CENTRES BEAR OUT PREDICTIONS?

Tertiary referral centres differ from regional hospitals because patients tend to be referred late in the disease course. As a result, all these centres have found dysplasia or cancer in a proportion of patients at the first "screening colonoscopy", usually approximately 15 years after onset [15, 23, 24]. Knowledge of appropriate action on the finding of dysplasia has evolved over the last two decades, and criticism should not be levelled at results published when knowledge of the clinical significance and limitations of dysplasia was at an exploratory stage. Operation was often delayed for patients with dysplasia with the result that carcinoma developed. This is illustrated by two series, in one of which carcinoma later developed in 39% of those with an initial diagnosis of dysplasia but only 1% of those without [23], and another in which 18% of those with initial dysplasia developed carcinoma later compared with only 3% of those without dysplasia [15].

The most recent report from a referral centre showed that 21 of 332 patients were operated upon for dysplasia or curable carcinoma. However, there were 4 cancer deaths during surveillance over a period of 20 years [15].

IS SURVEILLANCE COST-EFFECTIVE?

Patients value surveillance because it enables them to continue life with an intact colon. For them, the programme can be costed per patient year of follow-up without surgery. This is generally the cost of one clinical consultation, endoscopy and pathological examination of biopsies. In our series, this cost can be estimated from the numbers of investigations performed as £110 per year based on £150 for colonoscopy and £50 for sigmoidoscopy.

Health economists tend to judge effectiveness of surveillance as the cost of consultation and investigations leading to an operation for precancer or curable cancer. In our own series, this cost was about £13000 for each such operation, and another estimate from the U.K. was £6015 for each cancer diagnosed [25]. The cost per significant clinical finding was much greater in the other series from the U.K. because only one clinically significant abnormality was detected in 739 colonoscopies [22]. Whether or not these costs are judged as worthwhile depends on the health resources available.

ARE RECRUITMENT AND PATIENT COMPLIANCE ADEQUATE?

Two series have shown that recruitment of patients seen in hospital tends to be incomplete [15, 22]. One reason is that colitis judged initially to be distal in extent spreads insidiously so that extensive colitis is not recognised [25]. To avoid this failure of ascertainment, endoscopy is recommended for all patients with colitis 8–10 years after onset. Even so, not all patients will be recruited. Efforts at ascertainment and recruitment of all patients with extensive colitis in a community also tend to be unsuccessful [21].

Common life events which cause patients to desist from surveillance are that they leave the area, develop a coincidental illness, or find it difficult and inappropriate to attend due to the frailty of advancing age. The proportion of patients who left surveillance because they found the programme inconvenient or unwelcome was only 4% in our series [15].

IS COLONOSCOPY ESSENTIAL FOR SURVEILLANCE?

Examination of 50 protocolectomy specimens with carcinoma complicating ulcerative colitis showed that in 36 (72%) there was a tumour in the recto-sigmoid. Of 20 specimens (40%) with dysplasia in this region, there was a carcinoma proximally in 5 [2]. Thus, approximately three-quarters of patients with carcinoma have either a tumour in the recto-sigmoid or dysplasia in the distal colon which is associated with a proximal tumour. These findings are similar to other studies [26].

Flexible sigmoidoscopy should thus be effective in cancer surveillance, but so far this has not been tested. Colonoscopy is needed for examination of the whole colon, but a complementary role for the simpler, less uncomfortable and cheaper technique of flexible sigmoidoscopy in a surveillance programme has yet to be established.

RESPONSE TO SOME CRITICISMS OF CANCER SURVEILLANCE IN COLITIS

Precancer

Recent genetic research confirms the concept of a precancerous phase recognisable by chromosomal abnormalities (aneuploidy) and gene mutations or deletions. A corollary of the concept that a patchy clonal change occurs, which may differ in the type of genetic abnormality from one part of the colon to another, is that a particular genetic abnormality may be present or absent in one of these areas; all possible abnormalities are not even present in carcinoma. Dysplasia is a histologically visible manifestation of these changes; like other markers it may be present or absent in areas with genetic change. Unequivocal dysplasia when found is useful and reasonably specific. Problems arise because definitions of dysplasia with differing sensitivity and specificity are used.

Early carcinoma

Many reviewers quote early surveillance series as evidence of failure to diagnose carcinoma at a curable stage. Early series tended to be reported from referral centres with a high incidence

of dysplasia at the initial screening colonoscopy; neither doctor nor patients were confident about the clinical value of this finding or its time course. It is not appropriate to quote as results of surveillance clinical series described for another purpose, such as that which drew attention to dysplastic mass lesions [12].

Absence of positive findings

A series from Copenhagen is the only one in the literature to detect no excess cancer risk in colitis [27]. Contributory factors may be early and energetic medical treatment of acute attacks, prolonged use of 5-aminosalicylic acid derivatives in remission, an unusually high rate of surgical treatment early in the disease course, a relatively high proportion of patients with distal colitis, and a median follow-up of 11.7 years, which implies that almost half of the cohort of patients were in the first decade of disease. The finding of only one patient with high grade dysplasia/carcinoma during 709 patient years of follow-up in another series [22] is unexpectedly low as already discussed.

Expectation of universality and perfection

Cancer surveillance in colitis can only benefit those within the programme. The fact that ascertainment and recruitment of patients to the programme may be incomplete does not invalidate it. Cancer surveillance in other organs rarely eliminates cancer deaths. The aim in colitis should be to minimise the risk, hopefully reducing it to that expected in the general population.

Absence of controlled data

To demonstrate halving of the expected mortality rate from 8 to 4% among patients with extensive colitis followed for 25 years with an intact colon, a controlled trial would entail comparison of two groups of approximately 500 patients each, followed for at least 10 years. The ethical and administrative problems of such a trial would be considerable. Hopefully, case–control studies may be possible.

Cost

A widely quoted theoretical estimate of cost was based on a figure for colonoscopy which was four times that already quoted, annual colonoscopy, and a frequency of cancer half that generally accepted [28].

Reliance on detection of curable cancer by early investigation of symptoms

Our evidence [15] and that of others [25] suggests that symptomatic cancer in colitis tends to be at an advanced stage, perhaps because minor symptoms are attributed to colitis. There is currently no evidence that clinical supervision with early investigation of symptoms reduces cancer risk.

Analogies with colorectal cancer screening in the asymptomatic general population

Sufferers with colitis differ from the general public in one obvious respect. Patients are seeking medical help, and clinicians have a responsibility to limit the impact of the disease on their lives. Since a characteristic of cancer in colitis is that it tends to occur at an earlier age than in the general population, comparisons with screening among older age groups do not compare like with like.

CONCLUSIONS

(i) A reasonable expectation of finding clinically significant abnormalities during cancer surveillance in colitis is likely only in patients with extensive colitis of at least 10 years duration, a retained rectum after colectomy or perhaps in patients with cholangitis.

(ii) Dysplasia, despite its limitations, is a useful marker of precancer. Multiple biopsies from flat mucosa and targeted biopsies from suspicious areas are needed to give adequate sensitivity for its detection. Unequivocal dysplasia is sufficiently specific to warrant colectomy.

(iii) Failure to find dysplasia does not ensure that carcinoma is absent.

(iv) New markers of precancer are promising.

(v) Colonoscopy with multiple biopsies is a safe procedure for cancer surveillance in colitis.

(vi) Cancer surveillance in colitis is of unproven benefit, but recent results from regional hospitals are good. The cost-effectiveness appears acceptable in well developed health systems.

(vii) Flexible sigmoidoscopy is likely to have a role in surveillance but it is untested.

(viii) Ascertainment and recruitment of all patients with extensive colitis are likely to be incomplete. Patient compliance is adequate, but carcinoma which occurs among patients who leave surveillance will always limit results.

IS THE ORIGINAL PROPOSITION CORRECT?

Cancer surveillance in ulcerative colitis is not essential for every patient, but may minimise the cancer risk for the limited number with long-standing extensive disease who choose to accept it; colonoscopy is essential but the complementary role of flexible sigmoidoscopy has yet to be assessed.

1. Sugita A, Greenstein AJ, Ribeiro MB, *et al.* Survival with colorectal cancer in ulcerative colitis: a study of 102 cases. *Ann Surg* 1993, **218**, 189–195.
2. Connell WR, Talbot IC, Harpaz N, *et al.* Clinicopathological characteristics of colorectal carcinoma complicating ulcerative colitis. *Gut* 1994, **35**, 1419–1423.
3. Broström O, Löfberg R, Nordenvall B, Öst Å, Hellers G. The risk of colorectal cancer in ulcerative colitis: an epidemiological study. *Scand J Gastroenterol* 1987, **22**, 1193–1199.
4. Ekbom A, Helmick C, Zack M, Adami H-O. Ulcerative colitis and colorectal cancer: a population-based study. *N Engl J Med* 1990, **323**, 1228–1233.
5. Gilat T, Fireman Z, Grossman A, *et al.* Colorectal cancer in patients with ulcerative colitis: a population study in central Israel. *Gastroenterology* 1988, **94**, 870–877.
6. 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**, 800–806.
7. Broomé U, Lindberg G, Löfberg R. Primary sclerosing cholangitis in ulcerative colitis—a risk factor for the development of dysplasia and DNA aneuploidy? *Gastroenterology* 1992, **102**, 1877–1880.
8. D'Haens GR, Lashner BA, Hanauer SB. Pericholangitis and primary sclerosing cholangitis are risk factors for dysplasia and cancer in ulcerative colitis. *Am J Gastroenterol* 1993, **88**, 1174–1178.
9. Ransohoff DF, Riddell RH, Levin B. Ulcerative colitis and colonic cancer: problems in assessing the diagnostic usefulness of mucosal dysplasia. *Dis Colon Rectum* 1985, **28**, 383–388.
10. Taylor BA, Pemberton JH, Carpenter HA, *et al.* Dysplasia in chronic ulcerative colitis; implications for colonoscopic surveillance. *Dis Colon Rectum* 1992, **35**, 950–956.
11. Rubin CE, Haggitt RC, Burmer GC, *et al.* DNA aneuploidy in colonic biopsies predicts future development of dysplasia in ulcerative colitis. *Gastroenterology* 1992, **103**, 1611–1620.
12. Blackstone MO, Riddell RH, Rogers BHG, Levin B. Dysplasia-associated lesion or mass (DALM) detected by colonoscopy in long-standing ulcerative colitis: an indication for colectomy. *Gastroenterology* 1981, **80**, 366–374.

13. Butt JH, Konishi F, Morson BC, Lennard-Jones JE, Ritchie JK. Macroscopic lesions in dysplasia and carcinoma complicating ulcerative colitis. *Dig Dis Sci* 1983, **28**, 18–26.
14. Bernstein CN, Shanahan F, Weinstein WM. Are we telling patients the truth about surveillance colonoscopy in ulcerative colitis? *Lancet* 1994, **343**, 71–74.
15. Connell WR, Lennard-Jones JE, Williams CB, Talbot IC, Price AB, Wilkinson KH. Factors affecting the outcome of endoscopic surveillance for cancer in ulcerative colitis. *Gastroenterology* 1994, **107**, 934–944.
16. Melville DM, Richman PI, Shepherd NA, Williams CB, Lennard-Jones JE. Brush cytology of the colon and rectum in ulcerative colitis: an aid to cancer diagnosis. *J clin Path* 1988, **41**, 1180–1186.
17. Löfberg R, Broström O, Karlén P, Öst Å, Tribukait B. DNA aneuploidy in ulcerative colitis: reproducibility, topographic distribution and relation to dysplasia. *Gastroenterology* 1992, **102**, 1149–1154.
18. Harpaz N, Peck AL, Yin J, *et al.* p53 protein expression in ulcerative colitis-associated colorectal dysplasia and carcinoma. *Hum Path* 1994, **25**, 1069–1074.
19. Löfberg R, Broström O, Karlén P, Tribukait B, Öst Å. Colonoscopic surveillance in long-standing total ulcerative colitis: a 15-year follow-up study. *Gastroenterology* 1990, **99**, 1021–1031.
20. Leidenius M, Kellokumpu I, Husa A, Riihela M, Sipponen P. Dysplasia and carcinoma in longstanding ulcerative colitis: an endoscopic and histological surveillance programme. *Gut* 1991, **32**, 1521–1525.
21. Jonsson B, Åhsgren L, Andersson LO, Stenling R, Rutegård J. Colorectal cancer surveillance in patients with ulcerative colitis. *Br J Surg* 1994, **81**, 689–691.
22. Lynch DAF, Lobo AJ, Sobala GM, Dixon MF, Axon ATR. Failure of colonoscopic surveillance in ulcerative colitis. *Gut* 1993, **34**, 1075–1080.
23. Nugent FW, Haggitt RC, Gilpin PA. Cancer surveillance in ulcerative colitis. *Gastroenterology* 1991, **100**, 1241–1248.
24. Rosenstock E, Farmer RG, Petras R, Sivak MV Jr, Rankin GB, Sullivan BH. Surveillance for colonic carcinoma in ulcerative colitis. *Gastroenterology* 1985, **89**, 1342–1346.
25. Jones HW, Grogono J, Hoare AM. Surveillance in ulcerative colitis: burdens and benefit. *Gut* 1988, **29**, 325–331.
26. Choi PM. Predominance of rectosigmoid neoplasia in ulcerative colitis and its implications on cancer surveillance. *Gastroenterology* 1993, **104**, 666–667.
27. Langholz E, Munkholm P, Davidsen M, Binder V. Colorectal cancer risk and mortality in patients with ulcerative colitis. *Gastroenterology* 1992, **103**, 1444–1451.
28. Collins RH Jr, Feldman M, Fordtran JS. Colon cancer, dysplasia, and surveillance in patients with ulcerative colitis: a critical review. *N Engl J Med* 1987, **316**, 1654–1658.