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Cancer surveillance of patients with longstanding ulcerative colitis: a clinical, endoscopical, and histological study

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SUMMARY An eight year endoscopical and histological cancer surveillance programme comprising 71 patients with ulcerative colitis is presented. Forty one patients had total colitis and 30 substantial colitis. Mean duration of the disease was 19·7 years (range 9–46 years). An average of 2·6 colonoscopies per patient in the total colitis group were carried out, and at least two biopsies were taken at 10 locations in the colon. In the total colitis group, seven had either low (four), or high grade dysplasia (two), or Dukes' A cancer (one). In the group with substantial colitis two patients with low grade dysplasia were found. Dysplasia or cancer leading to operation was found above the rectum in four of five operated patients, all having had total colitis for 25 to 44 years. The dysplasia and cancer findings at the colonoscopy preceding surgery corresponded well with the surgical specimens. In three operated patients a sequence of dysplasia development was recorded. With the exception of long duration and dysplasia, nothing in the clinical course distinguished the operated cases. Using this surveillance programme prophylactic colectomy can be limited to patients in a high risk group developing dysplasia. The risk of missing a cancer before it becomes incurable seems to be low.

Patients with ulcerative colitis run an increased risk of developing colon carcinoma.[1–7] Those with long duration, extensive disease, and dysplasia in the colon have been considered as a particular high risk group. The cancer risk in epidemiologically defined populations seems to be rather low though still increased compared with the general population.[7] The methodological problems when trying to estimate the cancer risk including selection of patients, time period of study and geographical area are important.[8 9] Because of the cancer risk prophylactic colectomy after 8–10 years duration of extensive disease has been advocated.[5 10 11] Colectomy in itself, however, carries hazards and has to be balanced against the risk of cancer development. Cellular dysplasia of the colon often precedes cancer in ulcerative colitis.[12 13] A sequence of dysplasia development as a precursor of cancer has been postulated and has been supported by several clinical studies.[6 14–18]

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The aim of this investigation was to study patients with ulcerative colitis in order to select patients for prophylactic colectomy on the basis of dysplasia findings. Regular colonoscopies and sigmoidoscopies were carried out and multiple biopsies were taken in order to determine site, frequency, and development of dysplasia. Furthermore the value of sigmoidoscopy *versus* colonoscopy was evaluated.

Methods

PATIENTS

The basis of the study was all patients with ulcerative colitis attending the Department of Gastroenterology at South Hospital. All patients having radiological changes at least reaching the splenic flexure and with eight years duration or more of the disease were asked to participate in the surveillance programme. The diagnosis was made according to criteria defined by Evans and Acheson for definite ulcerative colitis.[19] An upper age limit of 70 years was set. The surveillance programme was initiated in January 1974 and the results until June 1982 have been evaluated.

SIGMOIDOSCOPY

Sigmoidoscopy was done twice a year or once, at year of colonoscopy. A rigid instrument was used and as a rule two to three biopsies were taken distally from 15 cm.

COLONOSCOPY

Colonoscopy was done every second year between eight and 20 years of duration, and thereafter annually. Fluoroscopy was used to confirm the site of the instument. Two biopsies were taken at each of 10 locations (Fig. 1). Further biopsies were taken when macroscopic lesions were found. If dysplastic changes were found, annual colonoscopies were carried out. Patients reaching 70 years of age during the programme and those who underwent colectomy with ileorectal anastomosis were further surveyed only by sigmoidoscopy.

BIOPSIES

When the surveillance programme started the cellular atypia was assessed in the classical way giving three grades—slight, moderate, or severe atypia. Atypia was only recorded when obviously not caused by inflammation. In 1983, however, this classification was changed by R H Riddell *et al.*[20] For ease of comparison it has been assumed that severe atypia corresponds to 'positive, high grade dysplasia' and moderate atypia to 'positive, low grade dysplasia'. Slight atypia corresponds to 'indefinite—probably positive (probably dysplastic)' and will be referred to as 'probably dysplastic' in the text.

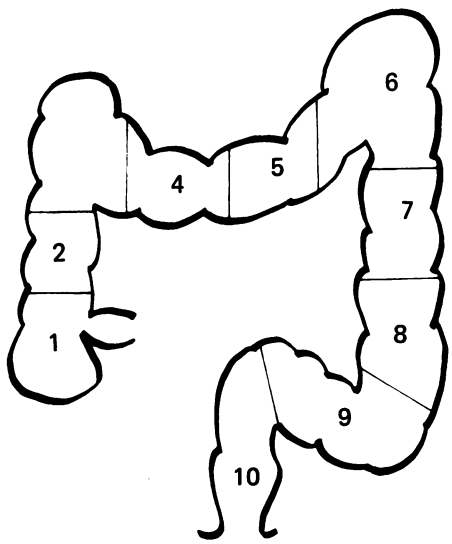

Fig. 1 *Colon divided into 10 segments for biopsy sampling at colonoscopy.*

All biopsies taken at colonoscopies and sigmoidoscopies were assessed by one pathologist (ÅÖ). In order to compare the grading level of dysplasia, most surgical specimens were also reviewed by two other specialised gastrointestinal pathologists. Their grading showed no major discrepancies from the original interpretation.

RADIOLOGY

The barium enemas which were mainly single contrast were evaluated according to signs of ulcerations or narrowing or shortening of the colon.

Most barium enemas (in 64 of 71 patients), were evaluated by senior radiologists within the same department of radiology at South Hospital. Radiographs that could not be traced were evaluated from the original report.

EXTENT OF DISEASE

The extent was evaluated according to a classification by Watts *et al*,[21] and thus based on radiological changes.

SUBSTANTIAL INVOLVEMENT

Mucosal changes in the rectum. Radiological changes in the distal colon reaching in proximal direction at the most to the hepatic flexure, and at the least as far as the splenic flexure.

TOTAL COLITIS

Mucosal changes in the rectum. Radiological changes in the entire colon or in proximal direction reaching at least beyond the hepatic flexure.

OBSERVATION PERIOD

Date of entry into study was defined as the year and month of the first colonoscopy. The end point in the individual cases was defined either as: patients under surveillance June 30th 1982 or last visit including sigmoidoscopy or colonoscopy and not heard from at least one year after, or proctocolectomy, or death.

SURGERY

Indications for surgery were findings of cancer, high grade dysplasia, low grade dysplasia with a macroscopic lesion or failure of medical therapy.

Results

PATIENTS

Originally 87 patients were eligible for the surveillance but 16 were discarded. Ten did not meet the criteria for definite ulcerative colitis and six of those in fact had Crohn's colitis. In six patients colonoscopy was not carried out for various reasons. Thus

71 patients, 36 women and 35 men, with the diagnosis of 'definite ulcerative colitis' remained for surveillance. Forty one had total colitis and 30 only substantial involvement. The mean age at diagnosis in the total colitis group was 24·6 years and in the substantial colitis group 36·5 years. Mean duration of the disease in the total colitis group at the end point of the study was 21·4 years and in the substantial colitis group 17·2 years.

FOLLOW UP

Five out of the 71 patients discontinued surveillance altogether; four because of other complicating diseases and one who was lost to follow up. In four patients colonoscopy surveillance was discontinued because of old age (>70 years) and those were subsequently followed only by rigid sigmoidoscopy.

COLONOSCOPY

One hundred and fifty two colonoscopies were undertaken; 2·6 colonoscopies per patient in the total colitis group and 1·5 in the substantial colitis group. Fourteen colonoscopies were incomplete. Seventeen of 41 patients in the total colitis group had at least three colonoscopies (range three to eight). There were no major complications such as bleeding or perforation.

DYSPLASIA

Degree, site and development

Seventeen patients had 'probable dysplastic' changes. At subsequent colonoscopies the changes were not found again in eight of 17 patients (five of 11 in the total colitis group) (Table).

In the total colitis group six patients developed low or high grade dysplasia and one had a Dukes' A carcinoma. In the substantial colitis group two patients developed low grade dysplasia.

In four of seven patients with total colitis who had at least low grade dysplasia, these findings were initially made above the rectum at colonoscopy. Five patients were operated upon because of dysplasia or cancer. Figure 2 shows the individual development of dysplasia at the colonoscopies preceding surgery and in the surgical sepcimens. The dysplasia or cancer leading to operation was found above the rectum in four of five patients. As can be seen in the figure, 'probable dysplastic' changes preceded more severe dysplastic changes in three of five patients. There was a good correlation of dysplasia findings between the surgical specimens and the preceding colonoscopies.

Table *Findings of dysplasia among 41 patients with total colitis and 30 with substantial colitis*

	Negative	*Probably dysplastic*	*Low grade*	*High grade*	*Cancer*
Substantial colitis	22	6	2	0	0
Total colitis	23	11	4(2)*	2(1)*	1

*Number of patients with dysplasia in a macroscopic lesion.

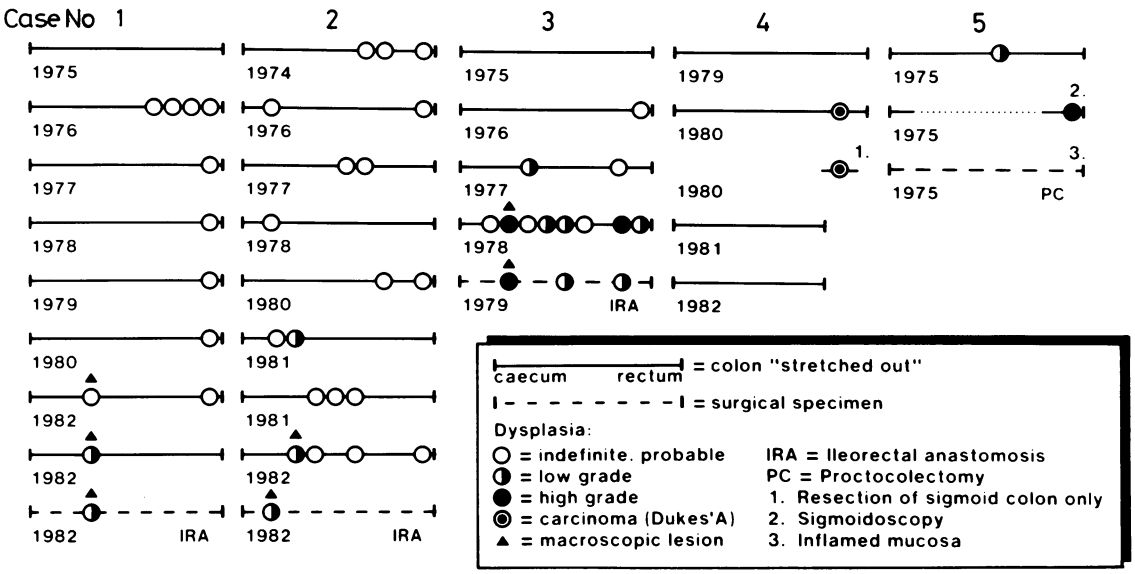

Fig. 2 *Consecutive findings of dysplasia in five operated patients at annual colonoscopies preceding surgery.*

The four patients with low grade dysplasia, who were not operated, were continued to be surveyed, but did not develop high grade dysplasia nor carcinoma during the study period. Two of these patients have had further colonoscopies, in one of those changes regressed to 'probable dysplasia' and in the other low grade dysplasia remained.

Operated patients with dysplasia – clinical features
Patient 1
A 50 year old man with 30 years duration of the disease with quiescent disease for many years. 'Probable dysplastic' changes were found both in the rectum and the left-sided colon and preceded the macroscopic lesion with low grade dysplasia in the transverse colon by six years. Ileorectal anastomosis was performed.

Patient 2
A 43 year old man with 27 years duration of the disease. The disease had a chronic intermittent course. 'Probably dysplastic' changes at various locations preceded the finding of a macroscopic lesion with low grade dysplasia at the hepatic flexure by seven years. Ileorectal anastomosis was performed.

Patient 3
A 53 year old man with 44 years duration of disease. He had had a chronic intermittent course. 'Probably dysplastic' changes and low grade dysplasia preceded extensive dysplasia of low and high grade including a macroscopic lesion at the hepatic flexure. Ileorectal anastomosis was carried out.

Patient 4
A 60 year old man with 30 years duration of the disease and remission for many years and with intermittent activity of sclerosing cholangitis. At the second colonoscopy a polypoid Dukes' A carcinoma was discovered without any preceding findings of dysplasia. Because of the surgeons preference, only sigmoid resection was carried out. Repeated postoperative colonoscopies have not shown any dysplasia.

Patient 5
A 42 year old woman with 25 years of the disease and a chronic intermittent course. Low grade dysplasia preceded high grade dysplasia in the rectum. Panproctocolectomy was therefore carried out. The surgical specimen was difficult to interpret because of inflammation of the mucosa but high grade dysplasia could be identified in the last portion of the colon.

Four more patients were operated, all because of failure of medical therapy. None of those had dysplasia.

DYSPLASIA AND DURATION OF DISEASE
Low and high grade dysplasia was never observed during the initial 15 years of disease. Macroscopic lesions did not appear until 27 years of duration.

DYSPLASIA AND CLINICAL FEATURES
Patients with low or high grade dysplasia neither differed from the rest with respect to severity of first attack, nor did they differ with respect to severity of clinical course or the frequency of sulphasalazine treatment. Most patients had been in remission during their observation period (185 of 241 patient years). Eight of nine patients, eventually found to have low or high grade dysplasia or cancer, were on sulphasalazine therapy during surveillance.

Discussion

This is a prospective study with regular sigmoidoscopies and colonoscopies, where a large number of biopsies have been taken. This has enabled the study of possible individual dysplasia development over a rather long period of time. As the number of patients lost to follow up has been low the bias of selection caused by dropouts has been small. This might partly depend on the small size of our surveillance group and that the patients came from a limited area (mostly Stockholm County) and only a few moved out during the study period.

The caecum was reached in 91% of the colonoscopies which is similar to other studies. Patients with incomplete colonoscopies represent a delicate problem as dysplasia might be missed. A supplementary barium enema should probably be done in such situations, although it only reveals macroscopic lesions. It is not known how many biopsies are needed to discover dysplasia with any particular degree of certainty. The distribution of dysplasia is patchy.[13] The fact that preoperative dysplasia findings correlated well with the findings in the surgical specimen and no unexpected dysplasia was found suggests that 20 biopsies is an adequate number.

The time interval between colonoscopies is a practical problem. The time sequence of dysplasia into invasive carcinoma is not known and probably shows considerable individual variations. Retrospective studies of surgical specimens with dysplasia with or without carcinoma suggests a rather short interval of about 2·4 years[13] between the appearance of high grade dysplasia and cancer.

In five of seven patients with total colitis and at least low grade dysplasia there was a progress from none or 'probably dysplastic' changes to higher degrees. Macroscopic lesions in three cases appeared within one year although in no case until after 27 years duration. 'Probably dysplastic'

changes preceded in these cases with several years. These findings support the theory of progressive development of dysplasia although they do not show the full sequence of development to carcinoma. The rapid development of macroscopic lesions supports the practice of annual colonoscopies especially as lesions of this kind have been reported to contain early stage carcinomas,[17] although we did not have any in our series.

Interpretation of dysplasia was done by one pathologist. His grading level of the surgical specimens with dysplasia compared well with two other pathologists' interpretation. This is in accordance with previous experience where interpersonal variation is small when the degree of dysplasia is high.[20]

DYSPLASIA FINDINGS

Slight changes such as 'probably dysplastic' are very frequent among our patients. It remains unclear, however, how many of these changes will later develop into higher degrees of dysplasia. Also in nearly half of the patients they were not discovered again at subsequent colonoscopies. Whether this is because of sampling error or represents a true regress is difficult to determine. Only 17% of our cases with total colitis had low or high grade dysplasia or cancer. The frequency of dysplasia varies in other reports.[6 15] Selection of patients, duration of disease and pathologists interpretation of biopsies are factors which influence those figures. In the substantial colitis group only two patients had dysplasia and only of low grade. Our findings are in accordance with most studies reporting high grade dysplasia and/or cancer almost exclusively in the total colitis group. There have been a few reports of cancer in substantial or left sided colitis as well, but after a longer duration than in total colitis.[22] Our group of substantial colitis patients had a somewhat shorter duration of the disease than our total colitis group. This makes it hard to tell from which time point patients with substantial or left sided colitis should be kept under surveillance. Surveillance should, if at all, perhaps start at a later stage in substantial disease. When the extent of the colitis is difficult to evaluate, it might be wise to treat the patients as having total colitis.

Patients with chronic continuous activity have been reported to run an especially high risk of developing cancer.[4] No patients with continuous activity were found in our study, as this category of patients are operated early in the course of the disease. The sulphasalazine prophylaxis may have reduced this group as well. There was no correlation with dysplasia development and clinical features, such as severity of first attack, attack years during study and regular sulphasalazine medication. Thus, in our experience these clinical features have no value in deciding which individual patients should have more or less frequent surveillance.

Cancer without preceding or accompanying dysplasia has been recognised by several authors and Riddell has estimated a 19% frequency in a group of patients with resected colitis cancer.[13] As a case in point our single patient with carcinoma had no dysplasia at the time of diagnosis, at surgery or after.

The aim of our surveillance was to detect precancerous dysplasia and operate before cancer had developed. In cases developing carcinoma without preceding dysplasia regular surveillance might detect the cancer at an early and curable stage, as in our case.

A majority of our findings of low and high grade dysplasia or cancer leading to surgery were done above the rectum level. Thus sigmoidoscopy has not contributed much to relevant findings of dysplasia and colonoscopy seems vital in a surveillance programme. In our present surveillance practice sigmoidoscopy has been omitted in patients having regular colonoscopy, where biopsies naturally are taken in the rectum. No patients developed an incurable cancer during the surveillance. If the policy of colectomy in patients with total colitis of 10 years duration or more, had been strictly enforced there should have been at least an additional 36 colectomies. The clinical decision in individual patients has to be balanced between the advantages and disadvantages of either approach. Surveillance allows the patient to keep his colon for a longer time, maybe his entire life. A risk for relapse of the disease and for developing cancer exists. Finally the anxiety and strain caused by repeated colonoscopies has to be taken into consideration.

Surgery eliminates the risk of cancer and of relapse. It carries a postoperative morbidity and mortality. Life with an ileostomy, especially in younger people, gives psychological problems and may induce sexual dysfunction. New methods of surgery including the ileoanal pouch with intact anal sphincter function may help to overcome these disadvantages.

When screening patients with longstanding ulcerative colitis for dysplasia indicating high risk for developing cancer slight changes such as 'probably dysplastic' are frequent. Low or high grade dysplasia is found less frequently, and is rarely located in the rectum initially, thus emphasising the need for colonoscopy in a surveillance programme.

By selecting patients with at least low grade dysplasia in connection with a macroscopic lesion for prophylactic surgery the risk of missing patients with an incurable carcinoma appears to be low.

Addendum

Since June 1982 until December 1984 38 more patients with total colitis have entered the surveillance programme. Altogether 79 patients with total colitis and long duration have been under surveillance. Two further patients have had low grade dysplasia, one of those with macroscopic lesions. No more cases with carcinoma have been detected.

References

1 Dawson IMP, Pryse-Davis J. The development of carcinoma of the large intestine in ulcerative colitis. *Br J Surg* 1959; **47:** 113–26·1.
2 Edwards FC, Truelove SC. Carcinoma of the colon. *Gut* 1964; **5:** 15–22.
3 de Dombal FT, Watts JM, Watkinson G, Goligher JC. Local complications of ulcerative colitis: Stricture, pseudopolyposis and carcinoma of colon and rectum. *Br Med J* 1966; **1:** 1442–47.
4 Samuelsson S-M. Ulcerative colitis in the county of Uppsala. Clinical, epidemiological and socio-medical aspects. [Dissertation]. *Acta Univ Upsalienis* 1976.
5 Kewenter J, Ahlman H, Hulten L. Cancer risk in extensive ulcerative colitis. *Ann Surg* 1978; **15:** 824–8.
6 Lennard-Jones JE, Ritchie JK, Morson BC, Williams CB. Cancer surveillance in ulcerative colitis. Experience over 15 years. *Lancet* 1983; **ii:** 149–52.
7 Broström O, Nordenvall B, Berglund M, Monsen U, Sörstad J, Hellers G. The risk of colon carcinoma in ulcerative colitis—a study of a defined population. *Scand J Gastroenterol* 1983; **18:** suppl 86:11.
8 Whelan G. Cancer risk in ulcerative colitis: Why are results in the literature so varied? *Clin Gastrenterol* 1980; **9:** 469–76.
9 Sackett DL, Whelan G. Cancer risk in ulcerative colitis. Scientific requirements for the study of prognosis. *Gastroenterology* 1980; **78:** 1632–35.
10 Mac Dougall IPM. The cancer risk in ulcerative colitis. *Lancet* 1964; **ii:** 655–8.
11 Dennis C, Karlsson KE. Cancer risk in ulcerative colitis: formidability per patient year of late disease. *Surgery* 1961; **50:** 568–571.
12 Morson BC, Pang LSC. Rectal biopsy as an aid to cancer control in ulcerative colitis. *Gut* 1967; **8:** 423–434.
13 Riddell RH. The precarcinomatous phase of ulcerative colitis. *Curr Top Pathol* 1976; **63:** 179–219.
14 Lennard-Jones JE. Morson BC, Ritchie JK, Shove DC, Williams CB. Cancer in colitis. Assessment of the individual risk by clinical a histological criteria. *Gastroenterology* 1977; **73:** 1280–89.
15 Granqvist S, Gabrielson N, Sundelin P. Thorgeirsson T. Precancerous lesions in the mucosa in ulcerative colitis. *Scand J Gastroenterol* 1980; **15:** 289–6.
16 Fuson JA, Farmer RG, Harok WA, Sullivan BH. Endoscopic surveillance for cancer in chronic ulcerative colitis. *Am J Gastroenterol* 1980; **73:** 120–6.
17 Blackstone MO, Riddell RH, Rogers BGH, Levin B. Dysplasia-associated lesion or Mass (DALM) detect by colonoscopy in longstanding ulcerative colitis: An indication for colectomy. *Gastroenterology* 1981; **80:** 366–74.
18 Kewenter J, Hulten L, Åhren C. The occurrence of severe epithelial dysplasia and its bearing on treatment of longstanding ulcerative colitis. *Am Surg* 1982; **195:** 209–213.
19 Evans JG, Acheson ED. An epidemiological study of ulcerative colitis and regional enteritis in the Oxford area. *Gut* 1965; **6:** 311–24.
20 Riddell RH, Goldman H, Ransohoff D *et al*. Dysplasia in inflammatory bowel disease: Standardized classification with provisionel clinical applications. *Hum Pathol* 1983; **14:** no 11.
21 Watts JMc K, de Dombal FT, Watkinson G, Goligher JC. Early course of ulcerative colitis. *Gut* 1966; **7:** 16–31.
22 Greenstein AJ, Sachar DB, Smith H *et al*. Cancer in universal and leftsided ulcerative colitis: factors determining risk. *Gastroenterology* 1979; **77:** 290–4.