

The Occurrence of Severe Epithelial Dysplasia and Its Bearing on Treatment of Longstanding Ulcerative Colitis

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One hundred twenty-four patients with extensive ulcerative proctocolitis were operated upon with proctocolectomy. The mean observation time was 10.3 years. Before surgery rectal biopsies were taken in all patients. The relationship between precancerous lesion in rectal biopsies and the presence of precancer and/or cancer in the rectum or colon in the removed specimen was evaluated. Thirteen out of 14 patients showed evidence of severe rectal dysplasia as well as severe dysplasia in the large bowel specimen, and five of these patients had a carcinoma as well. The 14th patient showed severe dysplasia only in the rectum as well as a rectal carcinoma. Of 110 patients without severe rectal dysplasia, 36 showed evidence of severe colon dysplasia, and three of these patients had a large bowel carcinoma as well. Only one patient had a large bowel carcinoma without evidence of severe dysplasia in the rectum or colon. Thus, nine patients out of ten with large bowel carcinoma showed severe dysplasia in rectum and/or colon. Four of these carcinomas were unknown before surgery. Although severe dysplasia in the rectal biopsy is a strong indication of a large bowel carcinoma (6/14), a negative rectal biopsy does not exclude a large bowel carcinoma (4/110). Proctocolectomy cannot be looked upon only as a prophylactic procedure in patients with severe dysplasia in the rectal biopsy, but also as an attempt to curative surgery, as large bowel carcinoma may have already developed in a considerable number of patients where precancer is diagnosed in biopsies.

THE PROGNOSIS IN PATIENTS with colorectal carcinoma developing in association with ulcerative colitis (UC) is generally considered to be poor, partly because of the difficulty in early diagnosis of carcinoma in these patients, but also since the patients are often young and the carcinomas highly malignant.^{4,14} Since the chances of cure of colitis carcinoma are poor, prophylactic proctocolectomy has been considered in the past to be justified in high risk patients, *i.e.*, when UC has been present for about ten years, in order to prevent the development of this complication. However, many physicians and surgeons have been unwilling to accept the view that the risk of cancer justifies preventive colectomy since approximately one-half to two-thirds of

these patients will never develop a carcinoma and, therefore, would have been subjected to an unnecessary operation. Thus, it was of great importance when Morson and Pang in 1967¹⁷ suggested that patients with UC who showed epithelial dysplasia in rectal biopsies were particularly prone to develop large bowel carcinoma. An expectant attitude to the management of patients with longlasting extensive colitis has since then been favored by some physicians.¹⁶ However, it soon became apparent that precancerous changes in the mucosa sometimes spared the rectum entirely even in the presence of a large bowel carcinoma.^{2,20} To increase the accuracy, regular colonoscopies with multiple biopsies were considered an important part of the supervision program.^{8,12,16} However, due to the great variation in the proportion of dysplasia in the rectum and colon, even in association with a coexisting carcinoma, the recommended supervision program, which has been accepted in some centers, still appears not to be without hazard.

The aim of the present investigation has been to evaluate the relationship between precancerous lesion in rectal biopsies and the presence of precancer and/or cancer in the removed colon specimen from patients who had undergone proctocolectomy for total UC. Thereby, we wanted to investigate if preoperative rectal biopsies alone could be used as a method to detect precancer/cancer in these patients.

Material and Methods

One hundred sixty-three patients with total ulcerative proctocolitis were operated upon with proctocolectomy between 1969 and 1977 at the Department of Surgery at the University of Göteborg, Sweden. Total colitis was defined as rectal involvement as shown by sigmoidoscopy and radiologic evidence of large bowel involvement extending at least to the right flexure. In 124 of these

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TABLE 1. *Histologic Findings in the Rectal Biopsies and the Large Bowel Specimens in 124 Patients with Total UC*

Rectal Biopsy	Large Bowel	Carcinoma
Precancer	13 Precancer	5
	1 No precancer	1
No precancer	36 Precancer	3
	74 No precancer	1

patients, one to five rectal biopsies were taken preoperatively and examined for the presence of precancerous lesion (severe dysplasia). The material also included patients who have been referred to the clinic from other parts of Sweden and two patients who were admitted for prophylactic colectomy because of precancer in the rectal biopsy. In the remaining 39 patients, no biopsies were taken mainly because the patients were operated upon for a subacute or an acute attack of the disease. The mean duration of the disease in the 124 patients was 10.5 years. All operative specimens were investigated carefully by the same pathologist (CÅ), according to a prospective protocol. At least five biopsies were taken from each of five different places of the large bowel corresponding to the ascending, transverse, de-

scending, and the sigmoid part of the colon and the rectum. Precancer or severe dysplasia was defined according to the criteria given by Morson and Pang and previously described by us.¹⁴

In order to determine the cumulative risk of developing precancer in a patient with total involvement of the colon, the concept of duration years was used. The patients began to contribute duration years from the year of onset of the disease up until they underwent proctocolectomy.

The duration years have been divided into five-year intervals. The total sum of duration years within the five-year periods 1-5, 6-10, 11-15, 16-20, and 21-25 was 523, 352, 215, 122, and 59 respectively. The calculations were made according to a method previously used for estimation of the cancer risk in extensive UC in the same clinic.¹⁵

Results

Precancer (*e.g.*, severe dysplasia) was demonstrated, in the rectal biopsies before operation in 14 of the 124 patients (11%). Following histopathologic examination of the colorectal specimen in these patients, the precancerous changes were restricted to the rectum in one patient who had a carcinoma in the rectosigmoid portion of the bowel. In the other 13 patients, precancer,

TABLE 2. *Details of Ten Patients with Carcinoma*

Sex	Age at Operation	Length of History at Operation	Site	Duke's Stage	Cancer Known/Susp Before Surgery	Precancer on Rectal Biopsy	Alive After Operation
M	18	6	Sigmoid colon	A	No	Yes	7.1
M	53	7	Hepatic flexure	B	No	No	3.0
			Sigmoid colon	B	Yes		
F	28	8	Transverse colon	A	No	Yes	8.8
M	49	19	Rectum	A	Yes	Yes	4.1
F	47	19	Coecum	A	No	Yes	3.1
M	46	20	Transverse colon	A	Yes	Yes	6.2
F	38	20	Transverse colon	C ₂	Yes	No	3.7
F	69	23	Rectum		No	Yes	Dead after operation
M	46	23	Sigmoid colon	C ₁	Yes	No	3.1*
F	46	28	Coecum	B	Yes	No	7.1

* Known recurrence.

was also demonstrated at different sites in the specimen, and in five patients, an invasive carcinoma was present as well (Table 1).

In the remaining 110 patients without epithelial dysplasia in the rectal biopsies before operation, precancerous lesions could be identified at other sites in the removed specimen in 36 patients, and three of the patients proved to have a carcinoma. One of these patients had two carcinomas in the large bowel. In 74 patients there was no precancer demonstrated either in the rectal biopsies or in the mucosa of the removed specimen. One of these patients had a carcinoma in the coecum (Table 1).

Thus, in 124 patients 11 carcinomas were found in 10 patients. Details of the ten patients with carcinoma are illustrated in Table 2. In four patients, all subjected to prophylactic proctocolectomy because of severe dysplasia in the rectal biopsy, the cancer was discovered unsuspectedly when the removed specimen was investigated. In two of these patients, the duration of the disease was six and eight years respectively. Both these patients are still alive seven and eight years after surgery. In the remaining six patients, a carcinoma was demonstrated on barium enema.

The duration of the disease, *i.e.*, the interval from onset of the disease to proctocolectomy, as well as the mean duration of the disease in patients with and without precancerous lesions and carcinoma, is listed in Table 3.

The cumulative probability of developing precancer over a 25-year period after onset of the disease appears in Figure 1, calculated by the actuarial method. The cumulative incidence of developing precancer 25 years after onset of the disease amounted to 74%.

Discussion

The relationship between precancer in the rectal biopsy and cancer in the large bowel is well documented.^{6,10,14,23} The true incidence of large bowel carcinoma in patients with severe dysplasia in the rectum is difficult to estimate as not all reports have been based upon a comparison of the microscopical findings in the rectal biopsy and the removed specimen. Such an assessment appears to be a prerequisite since a carcinoma in ulcerative colitis is not always macroscopically detectable and can remain undiagnosed until it manifests itself with barium enema at colonoscopy or clinically.³ Of 17 proven carcinomas from four different materials, ten were unknown before surgery (Table 4). In the present series no less than four out of six large bowel carcinomas were unknown before surgery in 14 patients with severe dysplasia in the rectal biopsy.

In their original publication, Morson and Pang¹⁷

TABLE 3. Length of History and Mean Duration at Operation in 124 Patients with and without Precancer in Rectum and/or Colon and in Patients with Carcinoma

	Duration of Disease						Mean Duration Years
	0-5	6-10	11-15	16-20	21-25	26	
No precancer n = 73	35	17	10	8	2	1	13 (3-32)
Precancer n = 41	6	15	8	4	4	4	8 (1-25)
Cancer n = 10		3		4	2	1	16 (6-23)

found a high correlation between the biopsy diagnosis of precancer and the appearance of precancer in the colectomy specimen, and it has been concluded that total colonoscopy with multiple biopsies would add but little in the majority of these patients.¹⁶ Cook et al.,² however, considered that the epithelial dysplasia frequently spared the rectum even in patients who had

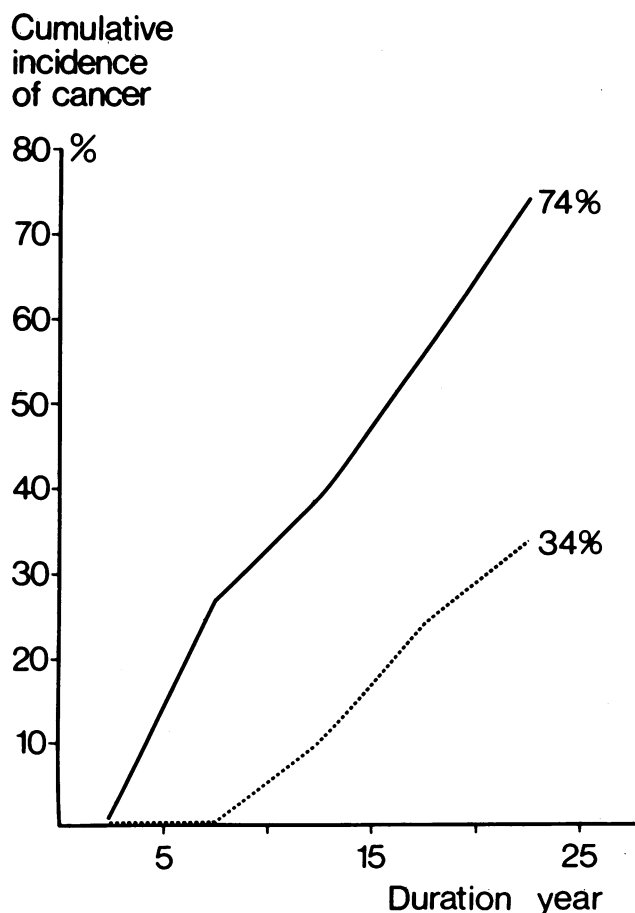


FIG. 1. Estimated cumulative probability of development of precancer and cancer (dotted) respectively in extensive ulcerative colitis. The figures for the estimated cancer risk from Kewenter et al.¹⁵

TABLE 4. Relation between Precancer in Rectal Biopsy and Large Bowel Carcinoma in Patients with Total Ulcerative Colitis

	Material	Dysplasia on Rectal Biopsy	Proctocol-ectomy	No. with Cancer	Cancer Unknown Before Surgery
Morson and Pang ¹⁷		9	9	5	1
Yardley-Keren ²⁴	41	3	3	2	1
Nugent et al. ²¹	80	16	10	4	4
Present material	124	14	14	6	4
		42	36	17	10

already developed a carcinoma elsewhere in the colon and considered a negative rectal biopsy as unreliable for screening purposes. Our results confirm theirs as four out of ten patients with carcinoma in the large bowel showed no precancer in the rectal biopsy. Furthermore, only 13 out of 49 patients with precancer in the large bowel showed precancer in the rectal biopsy. This may be due to a sampling error since the focus of severe dysplasia can be small in some patients²² and multiple rectal biopsies must always be taken to minimize this risk. Although a positive rectal biopsy is of great value in selecting patients, particularly at risk for developing carcinoma, a negative rectal biopsy is unreliable. The patient may have precancer or even an established cancer in the large bowel. A negative biopsy can create a feeling of false security both with the patient and the doctor.

The reported frequency of precancer in patients with a total UC varies widely.^{12,19,20,23} In patients with total involvement of the large bowel, the number of patients with precancer is correlated to the length of follow-up of each individual patient. Therefore, it is important to use appropriate statistical analysis when the risk of developing precancer and cancer in UC is discussed.^{5,6,7,13} In the present material, the risk to develop severe dysplasia in UC has been calculated with actuarial methods.^{5,6,13,15} As the patients were not followed up yearly with a rectal biopsy it might well be that the dysplasia may have occurred at an earlier stage than shown in the present material. The cumulative risk of developing carcinoma 25 years after onset of colitis symptoms was calculated at about 34% in material presented from the city of Göteborg as compared with a risk of 75% to develop precancer over the same period.¹⁵

Precancer in rectal biopsies has been considered as an absolute indication for prophylactic proctocolectomy by some authors, while others recommend surgery only

if severe dysplasia is consistent in more than one biopsy.^{10,16} To our mind colectomy is an absolute indication if severe dysplasia is found in one rectal biopsy, preferably present in the absence of marked inflammation, as six out of 14 patients with severe dysplasia in the rectal biopsy had invasive carcinoma in the removed specimen, and the carcinoma was unknown before surgery in four of the six patients.

It has been claimed that the need for prophylactic proctocolectomy in patients with longstanding total UC is unnecessary since these patients can be safely controlled by regular follow-up with colonoscopy and multiple biopsies.¹⁶ However, it has to be observed that about 30% of the patients with dysplasia in the rectum who underwent colectomy already had cancer, some of whom had already metastasized.²¹ Similar results have been found in other studies (Table 4). By adopting an expectant attitude with a regular follow-up system, thus delaying surgery until precancerous changes appear, a certain number of these patients will not be treated prophylactically. To our mind colonoscopy screening is not yet proven as an accurate security to patients that they do or do not belong to a high cancer risk group, particularly as carcinomas of the large bowel have been missed at colonoscopy.^{3,17,22}

An alternative approach for a high risk patient might be colectomy and ileorectal anastomosis. Patients with precancer restricted to the large bowel biopsies but with no precancer in the rectal biopsies might be candidates for such a procedure. Under these circumstances, an anastomosis should be done so that the entire rectum can be easily investigated by means of conventional proctorectoscopy. However, it has to be pointed out that the prognosis in patients with carcinoma developing in the rectum after IRA is gloomy,¹ and even tumors in the rectum, particularly the submucosa variety, may easily be overlooked. Large bowel carcinoma has also previously been reported in patients with mild as well as moderate dysplasia in the rectal biopsy.^{16,20} This opens the question whether patients with mild or moderate dysplasia should also be subjected to prophylactic surgery. The Lahey group are recommending colectomy for all patients with dysplasia.²⁰ To our mind proctocolectomy or colectomy with IRA should be considered very carefully also in these patients.

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