Clinicopathological characteristics of colorectal carcinoma complicating ulcerative colitis

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Abstract
This study examined three features associated with colorectal carcinoma complicating ulcerative colitis: (a) the distribution of 157 cancers in 120 patients with ulcerative colitis treated at St Mark's Hospital between 1947 and 1992; (b) the frequency at which dysplasia was found at a distance from the tumour in 50 total proctocolectomy specimens in which an average of 27 histology blocks were reviewed, and (c) the five year survival rate according to Dukes's stage and participation in a surveillance programme. Of 157 carcinomas, 88 (56%) occurred in the rectosigmoid, 19 (12%) in the descending colon or splenic flexure, and 50 (32%) in the proximal colon. Among the 120 patients, the rectum or sigmoid colon contained cancer in 81 (67.5%). Dysplasia was detected in 41 of 50 reviewed proctocolectomy specimens (82%). Dysplasia distant to a malignancy occurred in 37 (74%); two were classified indefinite, probably positive, 19 were low grade, and 16 were high grade; in 18 specimens there was an elevated dysplastic lesion. Survival was related to the Dukes's stage: about 90% of patients with Dukes's A or B cancer were alive at five years. The five year survival of 16 patients in whom cancer developed during surveillance was 87% compared with 55% of 104 patients who did not participate in surveillance (p=0.024).

Despite the large amount of published data regarding colorectal carcinoma complicating ulcerative colitis, details regarding the distribution of cancer and the frequency at which dysplasia occurs at a distance from the malignancy are controversial. These factors, together with the five year survival rate, have implications for the way in which clinicians treat patients with chronic extensive ulcerative colitis.

In contrast with a predominantly distal distribution seen in sporadic colorectal carcinomas, malignancy occurring in ulcerative colitis was originally reported to be distributed uniformly throughout the colon.1 2 More recent reports, however, have described a greater proportion of distal than proximal tumours in this condition.3-6 If this is the case, the use of fibreoptic sigmoidoscopy may have a role in endoscopic surveillance programmes.

The presence of dysplasia at a distance from cancer in ulcerative colitis was previously reported to be 96–100%.7 8 Two studies in the past decade, however, have described an absence of dysplasia in nearly 30% of colectomy specimens containing cancer in colitis.9 10 Because of this, the efficacy of endoscopic surveillance programmes using dysplasia as a marker of neoplasia has been questioned.11

Ultimately, the purpose of endoscopic surveillance in ulcerative colitis is to reduce the mortality of cancer associated with this condition. The overall five year survival rate after treatment of cancer in colitis is quoted as 31–55%.3 12-16 None of these reports distinguished patients whose cancer was diagnosed during surveillance.

We have examined our own series of patients with colorectal cancer in ulcerative colitis to assess the distribution of malignancy and the frequency at which dysplasia was detected distant to a tumour in recent total proctocolectomy specimens where complete sets of histological slides were available for review. In addition, the overall five year survival of those patients who did or did not participate in a surveillance programme was determined.

Methods

SELECTION OF CASES
The clinical and pathological records of all 120 patients with carcinoma complicating ulcerative colitis who were treated surgically at St Mark's Hospital between 1947 and 1992 were reviewed. This series includes some patients who have been previously described.17-19 The diagnosis and extent of ulcerative colitis were established radiologically, endoscopically or by review of the colectomy specimen.

EXAMINATION OF THE OPERATIVE SPECIMEN
At this hospital, fresh proctocolectomy specimens containing ulcerative colitis are normally opened longitudinally along the antimesenteric border, rinsed, photographed, and pinned to a board for 24–48 hours. The location of macroscopic lesions is recorded on a diagram of the entire specimen. In addition to sampling abnormal lesions, a continuous tram track of mucosa 1·0 cm in width is
obtained from the proximal to distal ends of the specimens. Paraffin wax sections of tissue blocks from the various colonic sites are than mounted on glass slides for histological examination, the sites of which are labelled on the diagram of the entire specimen. The tissue blocks measure at least 3 cm in length. Histological features of the carcinoma were recorded in accordance with the recommendations of the World Health Organisation.21

OCCURRENCE AND LOCATION OF DYSPLASIA
To review the distribution and frequency at which dysplasia occurred in specimens containing cancer in colitis, patients who had total proctocolectomy were identified. Specimens with available complete sets of histology slides suitable for review were selected.

Fifty sets of histology slides of proctocolectomy specimens obtained after 1962 were suitable for review. The site, stage, degree of differentiation, and grade of malignancy were reviewed by two pathologists (ICT, NB). Sections from the remainder of the colon were examined for the distribution and frequency at which dysplasia accompanied carcinoma and classified according to the recommendations of the Inflammatory Bowel Disease Morphology Study Group22 by two pathologists (ICT, NH). Dysplasia was defined as occurring adjacent to a tumour if it was detected on the same histology slide as the neoplasm. Dysplasia diagnosed on histology slides that did not contain malignancy was defined as being distant to the tumour, provided this site was greater than 3 cm from the neoplasm. The location of dysplasia was expressed according to the eight defined colorectal segments, namely caecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon or rectum.

PATIENTS RECEIVING SURVEILLANCE FOR CANCER
A surveillance programme for cancer in patients with chronic extensive ulcerative colitis was established at this hospital in 1966. Before 1971, this consisted of barium enema examinations and annual sigmoidoscopy and rectal biopsy. After 1971, surveillance included biennial colonoscopy and sigmoidoscopy in the intervening year. Cancer was diagnosed in 16 patients during surveillance who were treated surgically at St Mark’s.

FOLLOW UP AND SURVIVAL ANALYSIS
Complete five year postoperative follow up was available on all patients who developed cancer before 1988. The outcome of patients whose cancer occurred after this date has been evaluated up to 31 December 1992. Actuarial five year survival rates were determined in all 120 patients by Kaplan-Meier analysis. Survival according to Dukes’s stage was assessed in all patients. Overall five year survival rates were compared by log rank analysis between the 16 patients who developed malignancy during surveillance and the 104 patients whose cancer occurred outside a surveillance programme.

Results
CLINICOPATHOLOGICAL DETAILS OF ALL MALIGNANCIES IN 120 PATIENTS
One hundred and twenty patients with ulcerative colitis were treated for colorectal cancers between 1947 and 1992. Sixty two were male and the median age at diagnosis of cancer was 51 years (mean 50-1; range 21–86). The median age of disease onset was 27 years (mean 29; range 2–68). All but two patients had a history of colitis exceeding nine years before the development of cancer (median 19; range 0–58). The two exceptions were patients referred to St Mark’s for treatment of a known malignancy: in one, the diagnosis of ulcerative colitis was established at the same endoscopic examination that detected a malignant stricture of the rectum and the other was a patient referred for surgical treatment of a known tumour five years after the onset of ulcerative colitis.

Twelve malignancies were inoperable, and in these cases the primary tumour was not removed. The operation was palliative in 16 cases in which the tumour was considered to have been incompletely resected by the surgeon. Of the remaining 92 patients who had surgery with the possibility of cure, total proctocolectomy was performed in one or more stages in 66; colectomy and ileorectal anastomosis in five; proctectomy in 14; local excision in one; and segmental colonic resection in six.

There was clinical evidence of extensive colitis (inflammation proximal to the splenic flexure) in 107 patients, distal colitis in two patients, and in 11 the extent was impossible to assess because the resection was limited. Seventeen patients in whom distal colitis had been diagnosed before surgery developed cancer; at operation, 13 had extensive colitis, two had distal colitis, and in two the extent was not assessed (these patients had limited resections). Seven patients developed malignancy in a distal remnant 8 to 40 years after undergoing colectomy for disabling colitis; the rectum had been defunctioned in one and anastomosed to ileum in six.

Multiple synchronous cancers were found in 25 patients (21%); 18 with two tumours, four with three tumours, one with four tumours, and two with five tumours (total=157 carcinomas). Table I shows the location of these malignancies. Eighty eight tumours (56%) occurred in the distal colon (rectum or sigmoid colon), 19 (12%) in the descending colon or splenic flexure, and 50 (32%) were in the proximal colon.

Of the 120 patients in this series, carcinoma occurred in the rectum or sigmoid colon in 81 (67.5%). An additional seven patients had carcinoma in the descending colon or splenic flexure, giving a total of 88 patients (73.3%) with malignancy in the left colon.

| Table 1 Sites of cancer in 157 cancers of the bowel in 120 patients with ulcerative colitis |
|-----------------------------------------|-----------------|
| Rectum                                 | 70   |
| Sigmoid colon                          | 18   |
| Descending colon                       | 9    |
| Splenic flexure                        | 10   |
| Transverse colon                       | 18   |
| Hepatic flexure                        | 3    |
| Ascending colon                        | 23   |
| Caecum                                 | 6    |
| Total                                  | 157  |
Clinicopathological characteristics of colorectal carcinoma complicating ulcerative colitis

Figure 1: Distribution of dysplasia distant to a tumour in 50 total proctocolectomy specimens reviewed. Colectomy specimens of 37 patients contained dysplasia distant to a malignancy. Ten specimens had distinct dysplasia confined to the left colon, 10 to the right colon, and 17 had dysplasia in both left and right colon. The distribution of dysplasia within the left and right colon are shown.

REVIEW OF 50 PROCTOCOLECTOMY SPECIMENS

Histological details of malignancy

Adequate sets of histology slides from 50 proctocolectomy specimens of patients with cancer associated with ulcerative colitis were reviewed. The mean age of these patients was 49.7 years (range 23–82). Seventy-three carcinomas were detected; 33 were single tumours, in 13 cases there were two synchronous tumours, three patients had three cancers, and one had five synchronous malignancies. Tumour sites were rectum (27); sigmoid colon (nine); descending colon (one); splenic flexure (three); transverse colon (12); hepatic flexure (five); ascending colon (11); caecum (five). The Duke's stage for each cancer was A (42), B (15), C (16). No proctocolectomy specimens of patients with disseminated cancer were reviewed. Twenty-seven tumours (37%) were mucinous and 46 (63%) were non-mucinous. Thirty-two carcinomas were well differentiated, 31 moderately differentiated, and 10 poorly differentiated.

Dysplasia of colonic mucosa separate from cancer

These sets of histology slides from 50 colectomy specimens were also examined for dysplasia. All sections showing dysplasia occurred in mucosal areas that exhibited evidence of ulcerative colitis. The mean number of histology blocks per specimen examined was 27 (range 8–67; median 24).

Nine patients (18%) had no evidence of dysplasia in any of the histology blocks examined, including sites contiguous to a carcinoma. The mean number of histology blocks examined in these specimens was 22 (range 8–46; median 22). The mean age of these nine patients was 51.6 years (range 33–65). The sites of cancer were rectum (three), sigmoid colon (three), transverse colon (one), and ascending colon (two). All cancers were solitary; four were mucinous and five were non-mucinous. Six tumours were moderately differentiated, one well differentiated, and two poorly differentiated. Duke's stages were A (two), B (four), and C (two).

Dysplasia was diagnosed either adjacent to or at a distance from a tumour in 41 specimens (82%). This occurred contiguous in 39 (78%) and at a distance from a tumour in 37 (74%). Four cases had dysplasia contiguous to a tumour only; 35 had both contiguous and distant dysplasia and two cases exhibited distant dysplasia only. Of the 39 patients with dysplasia adjacent to a tumour, one was classified indefinite, probably positive, 17 were low grade, and 21 were high grade.

Of the 37 cases where dysplasia was diagnosed at a distance from tumour, two were classified indefinite, probably positive, 19 were low grade, and 16 were high grade. In 17 cases there was at least one elevated dysplastic lesion as well as dysplasia in flat mucosa; in one case there was a single elevated dysplastic lesion in the same segment as the tumour without dysplasia elsewhere. Distant dysplasia occurred in the same colonic segment as malignancy in 28 of 37 cases and in segments that did not contain cancer in 26 patients. Distant dysplasia was limited to one colonic segment in 12 specimens and occurred in more than one segment in 25.

Distant dysplasia was confined to the left colon (distal to the transverse colon) in 10 patients, to the right colon (proximal to the splenic flexure) in 10 patients, and occurred in both the right and left colon in 17 patients. Figure 1 shows the distribution of dysplasia in these 37 patients. It will be seen that 20 patients (40%) had dysplasia of the rectum or sigmoid colon. Fifteen of these 20 patients had rectosigmoid dysplasia at a distance from a tumour had carcinoma of the rectum or sigmoid colon; the other five patients had tumours occurring more proximally in the colon (Table II).

SURVIVAL ANALYSIS

The overall five and 10 year survival rates were 59.4% (95% confidence intervals 49.9 to 67.6%) and 55.3% (95% CI 45.4 to 64.1%). The worst stage of cancer in a given patient was Duke's A in 32, Duke's B in 33, Duke's C in 43, and disseminated in 12. Figure 2 shows the actuarial 10 year survival rates according to the worst stage for all patients. It will be seen that the five and 10 year survival

<table>
<thead>
<tr>
<th>Site of cancer</th>
<th>Patients (%)</th>
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<tbody>
<tr>
<td>Rectum or sigmoid colon</td>
<td>15</td>
</tr>
<tr>
<td>Splenic flexure</td>
<td>2</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>1</td>
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<tr>
<td>Ascending colon</td>
<td>2</td>
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<tr>
<td>Total</td>
<td>20</td>
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rates for stage A malignancy were 90.6% (95% CI 73.7 to 96.9%) and 82.2% (95% CI 61.6 to 92.3%) respectively; for stage B cancer 87.8% (95% CI 70.6–95.2%) and 87.8% (95% CI 70.6 to 95.2%) respectively; for stage C tumours 28.3% (95% CI 15.5 to 42.6%) and 22.7% (95% CI 9.9 to 38.6%) respectively and nil for disseminated malignancy.

The overall five year survival rate was compared in 16 patients who developed cancer during surveillance with 104 patients who did not participate in a surveillance programme. The overall five year survival rate in patients undergoing surveillance was apparently significantly improved compared with those in whom surveillance was not practised (87.1% vs 55.0% p = 0.024).

Discussion
Early series suggested that carcinoma complicating ulcerative colitis was uniformly distributed throughout the colon. Edwards and Truelove reported that the carcinoma occurred in the rectum in 22% of patients with ulcerative colitis compared with 36–40% occurring in the rectum of patients with sporadic colorectal cancer. In a different series, 39% of carcinomas complicating ulcerative colitis occurred in the rectum or sigmoid colon compared with 70% in the general population. More recent reports, however, suggest these tumours arise from the distal colon in 47–62% of cases.

Our series provides supporting evidence that the carcinoma in colitis usually occurs in the distal colon as 68% of patients (81 of 120) had a tumour occurring in the rectosigmoid and 73% (88 of 120) had malignancy distal to the transverse colon. It must be emphasised that these results may reflect a referral bias towards distal tumours, as a large proportion of our patients were referred for elective surgical treatment of a known malignancy. Acute presentation of malignancy, such as intestinal perforation or bowel obstruction, which is more likely to result from proximal colonic tumours was unusual at this hospital. The carcinoma risk in ulcerative colitis is considered to be greatest in patients with chronic extensive disease. Only two patients developed colorectal carcinoma less than nine years after the onset of symptoms of ulcerative colitis. In one of these cases, the two events are probably coincidental as bowel symptoms preceded the diagnosis of colitis and carcinoma by only two weeks. Only two of 111 patients in whom the extent of disease was assessed had distal colitis. The remaining 109 patients had clinical evidence of inflammation that extended proximal to the splenic flexure.

Seven patients developed cancer of a distal remnant 8 to 40 years after undergoing colectomy for disabling colitis; in one the rectum was defunctioned and in six it was anastomosed to ileum. Although such operations are sometimes a satisfactory and acceptable method for the treatment of colitis, the risk of cancer in the remaining rectum is well described. Regular surveillance of the rectal stump for dysplasia should be undertaken in any patient treated in this way.

The presence of dysplasia in the rectal biopsy specimens of patients with carcinoma of the colon was first seen by Morson and Pang. The true frequency at which dysplasia accompanies carcinoma in ulcerative colitis is uncertain. Ransohoff et al reported that 73% of colorectal carcinomas were associated with dysplasia at a distance from the tumour; in 50% this was high grade dysplasia. In the study in the Mayo Clinic, mucosal samples were examined from colectomy specimens containing carcinoma associated with ulcerative colitis using endoscopic biopsy forceps in a carefully planned manner so that four specimens were obtained at equal distances around the circumference of the colon at intervals of 10 cm along its length. Dysplasia was detected distant to malignancy in 74% of specimens: this was classified as high grade in 52%, low grade in 34%, and probably positive in 8%.

Our review of 50 proctocolectomy specimens entailed examination of an average of 27 histology blocks from various colonic sites. Dysplasia was absent in nine patients (18%), present adjacent to a tumour in 39 (78%), and distant from a malignancy in 37 (74%). There was no difference in the number of histology blocks examined in the specimens with and without dysplasia. Sixteen cases (32%) of distant dysplasia were high grade, 19 were low grade (38%), and two were indefinite, probably positive (4%). These results are virtually identical to those reported by Taylor et al.

Dysplasia at a distance from malignancy was detected equally in the right and left colon. Of 37 patients with distant dysplasia, dysplasia was confined to the left colon in 10, the right colon in 10, and in both the right and left colon in 17. Dysplasia at a distance from a tumour was detected in the rectum or sigmoid colon in 20 cases (40%); however, 15 of these cases had tumours occurring in the rectosigmoid and only five had tumours that were found more proximally (Table II).
It is still unclear if failure to detect dysplasia at a distance from malignancy in approximately 25–30% of patients with cancer associated with ulcerative colitis is a result of inadequate sampling or a true absence of this feature. Despite the rigorous sampling undertaken in this series and that previously reported by Taylor et al.10 the incidence of dysplasia was similar to the results obtained by Ransohoff et al.9 Except for an absence of multifocal tumours, there was no important difference in the clinical or pathological records in this series of patients to distinguish those in whom dysplasia was absent at a distance from cancer, from those in whom distant dysplasia was present. Results from an endoscopic surveillance programme suggest that patients without dysplasia at operation are those in whom dysplasia is not detected preoperatively.20 The weight of all this evidence suggests that, although a localised dysplastic lesion may precede development of a carcinoma, and may thus be potentially identifiable at a pre-cancerous stage, in about a quarter of cases no dysplasia is detectable at a distance from this site.

Although the prognosis of carcinoma occurring in ulcerative colitis had been previously regarded as grave,27 recent reports suggest that it is similar to sporadic colorectal carcinoma.12–16 Cumulative five year survival rates according to Duke’s stage in the 120 patients were 90-6% for Duke’s A tumours, 87-8% for Duke’s B tumours, and 28-3% for Duke’s C tumours. No patient with disseminated malignancy survived longer than one year. The 10 year survival rates were 82-2%, 87-8%, and 22-7% for Duke’s A, B, and C tumours respectively. These results, which are similar to other reports13 16 support the proposition that early diagnosis of cancer should improve survival.

While it has not been established that surveillance for cancer in ulcerative colitis is associated with an improved survival, we have assessed the respective outcomes of patients whose malignancy occurred during surveillance and those whose cancer developed outside a surveillance programme. The overall five year survival rate for the 16 patients whose cancer was diagnosed during surveillance was 87% compared with 55% of those who did not participate in surveillance (p=0.024). The number of cases developing cancer during surveillance was small and although this result is statistically significant, confirmatory evidence from other series is needed before it is concluded that surveillance improves survival in colorectal carcinoma complicating ulcerative colitis.

CLINICAL SIGNIFICANCE OF FINDINGS
Firstly, two thirds of patients with carcinoma complicating ulcerative colitis had tumours arising in the rectum or sigmoid colon. Among 40% of patients who had dysplasia in the rectosigmoid, one quarter had a tumour situated more proximally in the colon. Thus, almost 75% of patients with carcinoma in colitis had pre-cancer or cancer in the rectum or sigmoid colon. These findings support the use of flexible sigmoidoscopy in surveillance programmes as an additional investigation to colonoscopy, which would still be required to detect malignancy and dysplasia arising in the proximal colon. Secondly, the frequency at which dysplasia was reported by Taylor et al.10 the incidence of dysplasia was 74%. This result suggests that endoscopic surveillance using dysplasia as a marker of neoplasia will be unsuccessful in preventing carcinoma in almost one quarter of patients. New predictors of cancer are urgently required for this group of patients in whom no satisfactory marker of premalignancy is currently available. Thirdly, the five year survival varied according to the Duke’s stage of cancer, suggesting that as in sporadic colorectal carcinoma, early diagnosis will probably improve survival.