Colorectal Cancer in Patients with Ulcerative Colitis

A Prospective Cohort Study in Italy

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Background. The aim of this study was to assess the development of dysplasia or cancer in patients with ulcerative colitis and to determine the effectiveness of colonoscopy and biopsy follow-up in colon cancer surveillance.

Methods. From 1980 to 1986, 65 patients who had ulcerative colitis for 7 years or more participated in a surveillance program of colonoscopy and biopsy. This cohort was followed until December 1992. Forty-nine patients (75.4%) had extensive colitis and 16 (24.6%) left-sided colitis. The mean disease duration was 17.2 years. Three hundred four colonoscopies were performed. During each endoscopy, random biopsies were performed.

Results. Seven patients had definite dysplasia of the colorectal mucosa. Four of them had high grade lesions and underwent surgery. In all of these patients, colon cancer (3 Dukes' Stage A, 1 Dukes' Stage B) was found. No cancer was found in the other patients. Pedunculated adenomas were excised from 6 other patients during colonoscopy. When dysplasia was diagnosed, these patients were older than those who were dysplasia free, whereas the age at onset of colitis was significantly higher in the former (P < 0.01). Fifteen patients discontinued follow-up. Two of them developed colon cancer diagnosed at an advanced stage.

Conclusions. Dysplasia, especially of high grade, is a marker of colon cancer risk in patients with longstanding ulcerative colitis. Intensive colonoscopy and biopsy surveillance can lead to the diagnosis of colon cancer at a potentially curable stage. In this series, older age appeared to be an additional risk factor. A careful selection of patients with ulcerative colitis seems mandatory to minimize the cost and optimize the benefit of colon cancer surveillance programs. Cancer 1995;75:2045-50.

Key words: biopsy, colonoscopy, colorectal cancer, dysplasia, ulcerative colitis.

Ulcerative colitis (UC) is a disease that predisposes to the development of colorectal cancer.1-3 Patients at highest risk are those affected by colitis extending proximal to the splenic flexure and with more than 7-10 years of clinical history.2,4 Because dysplasia usually precedes the development of cancer in UC,5 this lesion has been proposed as a marker to detect patients with a particularly high risk of colorectal cancer.6,7 Several prospective studies are available in literature. Most authors suggest that endoscopic and biopsic surveillance of patients with UC could be useful in preventing fatal colon cancer.7-12 These works were performed mainly in Anglo-Saxon countries. Few data are available from Latin countries.

Thirteen years ago, we started a surveillance program of a cohort of patients with longstanding UC attending two referral institutions of Northern Italy. The main aim of this study was to assess the development of dysplasia or cancer in these patients and to determine the effectiveness and safety of colonoscopy and biopsy follow-up in decreasing colon cancer mortality of patients with UC living in our region.
Table 1. Characteristics of 65 UC Patients Included in the Surveillance Program

<table>
<thead>
<tr>
<th></th>
<th>Extensive colitis</th>
<th>Left-sided colitis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>49 (75.4%)</td>
<td>16 (24.6%)</td>
<td>65</td>
</tr>
<tr>
<td>Male/female</td>
<td>26/23</td>
<td>10/6</td>
<td>36/29</td>
</tr>
<tr>
<td>Age at admission (yr)</td>
<td>42.6 ± 13.9</td>
<td>48.9 ± 10.6</td>
<td>44.2 ± 13.4</td>
</tr>
<tr>
<td>Duration of UC (yr)</td>
<td>31.0 ± 12.3</td>
<td>38.6 ± 10.6</td>
<td>32.9 ± 12.2</td>
</tr>
<tr>
<td>Age at onset (yr)</td>
<td>31.0 ± 12.3</td>
<td>38.6 ± 10.6</td>
<td>32.9 ± 12.2</td>
</tr>
<tr>
<td>Total no. of colonoscopies</td>
<td>231</td>
<td>73</td>
<td>304</td>
</tr>
<tr>
<td>Colonoscopies per patient (mean, range)</td>
<td>4.7 (2-12)</td>
<td>4.6 (3-9)</td>
<td>4.7 (2-12)</td>
</tr>
<tr>
<td>Duration of follow-up</td>
<td>5.3 ± 3.5</td>
<td>7.6 ± 2.6</td>
<td>5.9 ± 3.4</td>
</tr>
</tbody>
</table>

UC: ulcerative colitis.

Patients

Over 500 patients with UC underwent colonoscopy from 1980 to 1986 in the Department of Medicine and Gastroenterology of the University of Bologna (Bologna, Italy) and in the Gastrointestinal Endoscopy Unit of the S. Giovanni A.S. Hospital in Turin, Italy. The diagnosis of UC was based on radiologic or colonoscopic and histologic findings. The extension of colitis was assessed by total colonoscopy and multiple biopsies.

One hundred seventy patients had long-standing UC (longer than 7 years). Eighty five of them had disease limited to rectum and sigmoid colon, whereas 95 were affected by extensive or left-sided colitis. Sixty-five of them participated in the surveillance program for colorectal cancer with repeated colonoscopies and biopsies (Table 1). Exclusion criteria for of the remaining 30 patients were: living in a geographic area far from Bologna or Turin (21 patients); refusing follow-up (5 patients); receiving a diagnosis of colon cancer at the first visit to our Institutions (4 patients, all Duke's Stage C2, 2 located in the left colon, the others in rectosigmoid area; mean duration of UC, 16 years). Patients with colon cancer diagnosed at first examination were excluded because our study did not focus on the colon cancer screening for UC.

Patients were enrolled from 1980 to 1986. The surveillance of this cohort of patients ended on December 31, 1992, or when a patient underwent proctocolectomy. Proctoscopy and biopsy examinations were repeated on patients with ileorectal anastomosis.

Methods

The extent of UC was evaluated based on the appearance of the large bowel by barium enema or by total colonoscopy and biopsies. Patients with UC proximal to the splenic flexure were considered to have extensive colitis, whereas the remaining patients were considered to have left-sided disease. Patients with involvement of rectum or rectosigmoid only were excluded from the study.

Colonoscopy and Biopsies

Total colonoscopy and biopsies were performed at admission. Thereafter, endoscopic and biotopic surveillance of patients with left-sided UC generally was limited to the left colon. After the first examination, patients were examined yearly or every 2 years. When dysplasia was found, colonoscopy was repeated after a shorter interval.

At each colonoscopy, two biopsies were taken from flat mucosa at the following sites: cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon; four specimens were taken from the rectum. Additional samples (at least four) were taken from any area with a macroscopic abnormality of the mucosa. Other rectal biopsies were performed to analyze kinetics of rectal epithelial cells. The results of this ancillary study have been published elsewhere.13

Biopsies were performed with standard miniforceps while pedunculated adenomas were excised by electrocoagulation during endoscopy. A mean of 19 diagnostic biopsies (range, 13–31 biopsies) were performed at each endoscopy. They were fixed in 10% buffered formalin and embedded in paraffin. Two experienced pathologists (G.B. and M.R.) separately examined the slides.

Dysplasia was identified according to the criteria of the Inflammatory Bowel Diseases Study Group.14 The specimens obtained before 1983 were reexamined blindly and classified according to these criteria.

Three main categories were recognized: negative,
positive, or indefinite for dysplasia. Biopsies positive for dysplasia were further classified in low or high grade. Uncertain findings were in turn subdivided into groups of probably positive or probably negative for dysplasia. Dysplastic lesions with a typical pedunculated polypoid shape were defined as adenomas. If they were not accompanied by mucosal dysplasia elsewhere, they were considered coincidental findings and were, therefore, considered separately.

Surgery

Indications for surgery were: failure of medical therapy, high grade dysplasia or malignancy, or colon stenosis.

Statistical Analysis

The cumulative risk to develop definite dysplasia was calculated using the life-table method. Differences in age, age at UC onset, or disease duration were evaluated by the Mann–Whitney U test.

Results

Patients

Forty-nine patients (75.4%) had extensive colitis, and 16 (24.6%) had left-sided colitis (Table 1). At the time of diagnosis, the mean age was 42.6 ± 13.9 years in patients with extensive colitis and 48.9 ± 10.6 years in the group with left-sided colitis. The mean duration of the colitis at the beginning and at the end of the study, respectively, was 11.6 ± 6.1 years and 17.0 ± 7.0 years, for extensive colitis, and 10.4 ± 4.0 years and 17.9 ± 5.6 years for left-sided colitis.

Colonoscopies

Two hundred thirty one total colonoscopies were performed on patients with extensive colitis and 73 on patients with left-sided colitis. The mean number of total colonoscopies per patient was 4.7 (range, 2–12 colonoscopies) for extensive colitis and 4.6 (range, 3–9 colonoscopies) for left-sided colitis. The mean duration of follow-up was 6.5 years (range, 4–12 years) (Table 1).

Follow-Up

Nineteen patients discontinued the follow-up, 14 underwent surgery, and 32 continued the surveillance program (Fig. 1). Among patients who discontinued the follow-up, two died of breast cancer. Two patients continued their care in another hospital. Fifteen patients refused further colonoscopies. Two of them, affected by extensive colitis, developed invasive colon cancer 4 and 6 years after their last follow-up colonoscopy.

Dysplasia

No dysplasia was found at first coloscopy in each case (Table 2). Forty seven patients remained negative for dysplasia during surveillance period. The mean age at the end of follow-up in these patients was 49.2 ± 14.8 and the mean duration of ulcerative colitis was 16.4 ± 7.0. Dysplasia was found in seven patients (six with extensive colitis, one with left-sided disease), and was high grade in four and low grade in three. High grade dysplasia was found on villous plaques (three patients) or on a polypoid mass (one patient). In three patients, low grade dysplasia always was observed on flat mucosa. For six patients, histologic findings uncertain for dysplasia were reported. Observers disagreed about three of six findings uncertain for dysplasia. Acute inflammation in the mucosa was suggestive of a decision of the probably-negative-for-dysplasia group. Dysplasia or uncertain for dysplasia was found in the ascending colon (five patients), in the transverse colon (two patients), in the descending colon (one patient), and in the rectum (five patients). Isolated pedunculated adenomas were found in five patients (three with extensive colitis) and were located in the cecum (one patient), in the transverse colon (one patient), and in the rectum-sigmoid area (3 patients). All these polyps were found in the affected mucosa.

All patients with high grade dysplasia showed low grade dysplasia arising on macroscopic lesions at biopsies taken 1–3 years before the high grade diagnosis
Table 2. Distribution of Dysplasia in 65 UC Patients Included in the Surveillance Program

<table>
<thead>
<tr>
<th></th>
<th>Extensive colitis (n = 49)</th>
<th>Left-sided colitis (n = 16)</th>
<th>Total (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No dysplasia</td>
<td>34 (69.4)</td>
<td>13 (81.2)</td>
<td>47 (72.3)</td>
</tr>
<tr>
<td>Definite dysplasia</td>
<td>6 (12.2)</td>
<td>1 (6.2)</td>
<td>7 (10.8)</td>
</tr>
<tr>
<td>Low grade</td>
<td>2 (4.1)</td>
<td>1 (6.2)</td>
<td>3 (4.6)</td>
</tr>
<tr>
<td>High grade</td>
<td>4 (8.2)</td>
<td>0</td>
<td>4 (6.2)</td>
</tr>
<tr>
<td>Uncertain for dysplasia</td>
<td>6 (12.2)</td>
<td>0</td>
<td>6 (9.2)</td>
</tr>
<tr>
<td>Adenomatous polyp</td>
<td>3 (6.1)</td>
<td>2 (12.5)</td>
<td>5 (7.7)</td>
</tr>
</tbody>
</table>

UC: ulcerative colitis.
Values in parentheses are percentages.

(Table 3). Uncertain findings or low grade dysplasia in flat mucosa were not constantly found at subsequent examinations.

Finally, pedunculated adenomas were excised during endoscopy. Neither dysplasia nor cancer was detected in these patients 3–10 years after polypectomy.

The mean duration of the disease, the age at diagnosis of lesions or at the end of follow-up, and the age at onset of UC were similar in patients without dysplasia and in patients with pedunculated adenomas or who were uncertain for dysplasia. Conversely, the mean age at diagnosis of dysplasia was higher, though not significantly, than the mean age at the end of follow-up in patients without dysplasia (56.7 ± 5.3 vs. 49.2 ± 14.8 years, respectively; P = NS). The disease duration was shorter for patients with dysplasia than for those who were dysplasia free (11.5 ± 2.5 vs. 16.4 ± 7.0 years, respectively; P < 0.05). The age at onset of colitis was significantly higher in patients with dysplasia than those without lesions (45.1 ± 6.1 vs. 32.7 ± 12.0 years, respectively; P < 0.01) (Fig. 2).

The cumulative proportion of patients who were dysplasia free decreased with the disease duration (Fig. 3). The trend toward a decrease was restricted to a duration ranging from 7 to 15 years. No further decrease was found beyond this limit. The result was probably related to the low number of patients with greater than 15 years of clinical history of UC.

Surgery

Fourteen patients underwent surgery. Indications for surgery were high grade dysplasia in four patients, intractable disease in seven, intractable disease and low grade dysplasia in one, and stenosis of the colon in two. Eight patients underwent ileoanal anastomosis, five received ileorectal anastomosis, and one received proctocolectomy with definitive ileostomy. All patients with high grade dysplasia had cancer (Table 3). The age at surgery was 50–64 years. In two patients (Patients 1 and 3), cancer was found in the same area of the biopsy specimen. In the other two patients (Patients 2 and 4), cancer was found far from the dysplastic lesions and was not detected at colonoscopy. In three patients with

Table 3. Clinical Details of Four UC Patients Operated on for High Grade Dysplasia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Duration at surgery (yr)</th>
<th>Age at surgery (yr)</th>
<th>Dysplasia before last colonoscopy</th>
<th>Dysplasia leading to surgery</th>
<th>Surgical procedure</th>
<th>Surgical specimen</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>64</td>
<td>LG-DALM (villous plaque) rectum</td>
<td>HG-DALM (villous plaque) rectum</td>
<td>Segemental resection</td>
<td>Dukes A cancer (HGD rectum)</td>
<td>Further LG and HG (rectum) Alive after 7 yr</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>50</td>
<td>LG-DALM (villous plaque) splenic flexure</td>
<td>HG-DALM (villous plaque) splenic flexure</td>
<td>IRA</td>
<td>Dukes A cancer (cecum) HG-DALM (splenic flexure) LG-DALM (transverse colon)</td>
<td>Further LG (rectum) Alive after 7 yr</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>61</td>
<td>LG-DALM (polyp) ascending colon</td>
<td>HG-DALM (polyp) ascending colon</td>
<td>IRA</td>
<td>Dukes A cancer (HGD ascending colon) LG-DALM (descending colon)</td>
<td>Decreased for primary lung cancer after 2 yr</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>63</td>
<td>LG-DALM (villous plaques) transverse colon</td>
<td>HG-DALM (villous plaques) transverse colon</td>
<td>IRA</td>
<td>Dukes B cancer (cecum) LG- and HG-DALM (transverse colon)</td>
<td>No further dysplasia Alive after 7 yr</td>
</tr>
</tbody>
</table>

UC: ulcerative colitis; LG: low grade dysplasia; HG: high grade dysplasia; DALM: dysplasia-associated lesion or mass; IRA: ileorectal anastomosis.
cancer (Patients 2–4), multiple foci of high grade dysplasia were scattered in other parts of the large bowel. The Dukes' Stage was A in 3 cases (Patients 1–3) and B in one case (Patient 4). Three patients with cancer underwent ileorectal anastomosis and one underwent a partial resection of the sigmoid colon. They all continued surveillance. Recurrence of dysplasia was found in two cases. One patient died from primary lung cancer 2 years after surgery.

Patients who underwent surgery for medical indications had no dysplasia in the resected specimens except for the patient with intractable disease and low grade dysplasia, whose colon had other foci of low grade lesions on flat mucosa.

**Discussion**

Some authors suppose that colon cancer is not a frequent complication of UC in Latin or Mediterranean countries. It has been suggested that environmental factors and probably diet can play a protective role against cancer in both patients with UC and in the general population. In our study, 7 of 65 patients with long-standing UC (10.8%) had definite dysplasia, and among them, 4 (6%) developed cancer during the follow-up. These figures are similar to those reported in Anglo-Saxon countries. Therefore, we believe that dysplasia or cancer in UC should not be disregarded or underestimated in our geographic area.

Our results also support the concept that dysplasia can be considered a marker of colon cancer risk in patients with UC. High grade dysplasia always was associated with cancer and was preceded by low grade dysplasia arising on macroscopic lesions. This agrees with the hypothesis of a progression of severity of dysplasia up to cancer development and the concept that dysplasia arising on macroscopic lesions are lesions at high risk for malignancy.

Conversely, pedunculated adenomas without dysplasia in other areas of the colon are not suggestive of a particularly increased colon cancer risk. At subsequent endoscopic and biopptic examinations (for periods from 3 to 10 years), dysplasia was not found in the five patients with previous adenoma. Therefore, a conservative approach to managing these patients is justified.

We found dysplasia in one patient with left-sided colitis. This finding suggests that patients with this condition also are at risk for colon cancer. A recent report indicates that patients with extensive and left-sided disease share the same risk of development of dysplasia.

In our cases, age appeared to be an additional risk factor for colon cancer in UC. Patients with dysplasia were older than those without lesions. Moreover, patients with dysplasia had a shorter mean duration of UC and a higher mean age at onset of UC than did patients without lesions. Finally, patients with UC with cancer were in an age range in which the risk for developing colon cancer was also high in the general population of our area. Concurring with others, we believe that this pattern is suggestive of a group of patients with an increased susceptibility for colorectal cancer, maybe genetically determined, but relating to the same exogenous factors as those present in the general population.

The mean follow-up of this study was a relatively short interval. Additional long-term follow up will confirm the validity of biopptic surveillance as a method for controlling carcinoma. However, the results suggest that the short-term risk of carcinoma in patients with negative biopsies is low and that colectomy for risk of carcinoma can be delayed in this group.

Because cancer always was diagnosed at an early...
stage, the results of our study are quite reliable. However, one should consider that they were obtained with intensive follow-up by colonoscopy and biopsy. Although we cannot know whether this intensive surveillance program is also cost-effective, we should underline that 2 of 15 patients who refused sequential colonoscopies developed invasive cancer. This failure of compliance was a relevant problem in our study as it also was in other series. A possible solution may be to optimize the selection of patients for enrollment in a surveillance program. Due to a lack of phenotypic or biochemical markers of individual cancer risk that are more sensitive than dysplasia, the follow-up planning only could be based on a thorough clinical risk evaluation. In populations such as ours, for example, patient age could affect the surveillance program. If we had restricted our recruitment to patients older than 45 years, we should have diagnosed all dysplasias and early cancers, spared many colonoscopies (and money), and probably increased the compliance rate.

References