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Is Colonoscopy Alone Sufficient to Screen for Ulcerative Colitis-associated Colorectal Carcinoma?

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Abstract. Patients with ulcerative colitis (UC) are at increased risk for colorectal carcinoma (CAC). Despite the fact that patients at risk are followed closely by colonoscopy to screen for dysplasia, the prevalence of CAC is still unacceptably high. The aim of this study was to evaluate the prevalence of risk factors for CAC, such as dysplasia, and to determine the relevance of colonoscopic surveillance in the group who went on to develop cancer. A series of 24 patients with UC were diagnosed with CAC. The patients' records were analyzed retrospectively for duration of UC, prevalence of preoperative dysplasia, and other cancer risk factors (CRFs) (e.g., pancolitis, primary sclerosing cholangitis, early onset of UC, and backwash ileitis). The mean age of the patients at the time of cancer diagnosis was 43 years with an average UC duration of 15 years (6 patients had had UC less than 8 years). CAC was identified preoperatively by colonoscopy in 15 of 24 patients, with an additional 7 of 15 showing flat dysplasia. Five of nine patients without preoperatively diagnosed CAC had flat dysplasia. Overall, 19 patients had additional CRFs, most of them with at least two more CRFs. Despite a regular colonoscopic follow-up for most patients with UC, flat dysplasia was missed in 12 patients preoperatively. Therefore we suggest that patient information should also always include surgical options in each case where significant cancer risk factors are found.

Patients with chronic ulcerative colitis (UC) have an increased risk of developing colorectal carcinoma (CAC) [1–6]. Moreover, it is presumed that the risk increases within the range of 0.5% to 1.0% per year after 8 to 10 years of disease in patients with extensive UC [7], so the risk of CAC increases from 1% to 3% at 10 years after diagnosis, to approximately 10% after 20 years, and to 25% after 35 years in patients with pancolitis [8–10].

The effects of long-term duration and the extent of the disease as risk factors for malignant transformation have been confirmed in several studies [5–11]. Recent publications also suggest that UC patients with primary sclerosing cholangitis (PSC), early age of onset of UC, and backwash ileitis are at increased risk for CAC [11–18]. By identifying and validating these and still unknown risk factors associated with CAC in patients with UC, risk assessment, surveillance strategies, and timing of indications for prophylactic surgery may be improved.

So far, surveillance programs that include colonoscopy and random biopsies have been recommended with the aim of detecting dysplasia as a malignant transformation at an early stage of carcinogenesis. Nevertheless, there is still controversy about the effectiveness of surveillance [1, 18–20], and the overall prevalence of manifest CAC in patients with UC remains unacceptably high [4, 21–23]. Several factors may be responsible for this unchanged incidence of CAC, including failure to undergo surveillance or the early development of cancer before surveillance is initiated. Noncompliance with surveillance recommendations is almost certainly more likely in patients with long remissions, although the risk of malignancy may not be influenced by a defined disease status [24]. Furthermore, it is well documented that cancers can certainly arise, despite perfect surveillance compliance, owing to biopsy sampling errors, incorrect or equivocal pathologic assessment, or even a true absence of associated dysplastic lesions [25]. Because of its flat appearance at an early stage, CAC arising from dysplastic lesion is often misdiagnosed, and delayed diagnosis of then advanced CAC during a surveillance program has been shown [19, 26]. Given these observations, the aim of this study was to analyze our series of patients with CAC for the prevalence of preoperative dysplasia and other cancer risk factors and thereby to determine the pitfalls of colonoscopy-based surveillance in patients suffering from UC.

Patients and Methods

The patient database of the Department of General Surgery at the University of Muenster, Germany was retrospectively searched for patients with UC and concomitant CAC treated between 1975 and February 2001. The records were reviewed, and 26 patients were found who had UC and concomitant CAC. In all 26 patients the diagnosis of UC was established before the detection of cancer.

Additional preoperative colonoscopy was performed in 92% of patients (24/26). The two patients without preoperative colonoscopy had undergone their last colonoscopy more than 5 years be-

The first two authors contributed equally to the presented data.

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Table 1. Demographic, clinical, and pathologic data for patients with CAC.

No. of patients	24
Age at UC diagnosis (years)	35 (12–52)
UC duration < 8 years (no.)	6
Disease severity (surgical specimen) (no.)	
Mild or moderate	11
Quiescent	5
Severe	8
Dysplasia at preoperative colonoscopy (no.)	12/24
DALM at preoperative colonoscopy (no.)	15/24
CAC at preoperative colonoscopy (no.)	15/24

UC: ulcerative colitis; DALM: dysplasia-associated lesion and mass; CAC: ulcerative colitis-associated colorectal carcinoma.

fore detection of cancer and were therefore excluded from further analysis. In 14 patients (58%) endoscopies were performed for surveillance, whereas 10 patients (42%) underwent colonoscopy because of significant changes in their symptoms. These changes included a significant alteration in bowel habits (diarrhea or obstruction) in six patients, increased bleeding or anemia in two patients, increased abdominal pain in four patients, and significant weight loss in three patients.

One to four random biopsy specimens at approximately 10-cm intervals were obtained during preoperative colonoscopy in 15 patients. In the other nine patients, one to three random biopsy specimens were obtained from various parts of the colon (cecum, ascending colon, transverse colon, descending colon, sigmoid, rectum). Additional biopsies were performed in all patients if suspicious lesions were observed.

In 14 patients (group I) colonoscopy was performed during the 2 years prior to preoperative colonoscopy, in 5 patients (group II) the last colonoscopy took place 2 to 5 years prior to preoperative colonoscopy, and in 5 patients (group III) no colonoscopy was done during the last 5 years prior to preoperative colonoscopy.

The demographic data, medical assessment, and treatment, as well as the presence of preoperative flat dysplasia, a dysplasia-associated lesion or mass (DALM), or polyps, other cancer risk factors, and pathology reports were analyzed.

Results

Demographic, clinical, and pathologic data for patients with CAC are summarized in Table 1. Sixteen patients (67%) were male and eight (33%) were female; the mean age at the time of surgery was 43 years (range 19–72 years). The mean duration of UC was 15 years (2–32 years), with six patients (25%) having documented UC for less than 8 years before their cancer diagnosis.

We found a positive family history for colorectal cancer in 3 of 19 (16%) patients, whereas in the remaining 5 patients there was no information regarding family history. According to pathology reports, two-thirds of the patients had either mild to moderate (46%) or quiescent (21%) colitis. Only 33% of patients had severe colitis.

The diagnosis of cancer was established preoperatively by endoscopy in 62.5% (15/24) of patients, among whom six cancers arose in polyps. DALMs were observed in 15 of 24 patients by preoperative colonoscopy; 7 patients with a preoperative CAC diagnosis showed additional flat dysplasia. In the 37.5% (9/24) of patients without a preoperative CAC diagnosis, 56% (5/9) showed flat dysplasia in biopsy specimens obtained by preoperative colonoscopy.

Table 2. Tumor stages in 24 patients with CAC (UICC classification).

	No. of patients			
Group	UICC I	UICC II	UICC III	UICC IV
I (n = 14)	2	5	6	1
II (n = 5)	0	2	1	2
III (n = 5)	0	2	3	0

UICC: International Union Against Cancer [27].

Table 3. Additional cancer risk factors for CAC in 19 patients.

Risk factor	No. of patients
Pancolitis	18
Early onset of UC	5
Duration of UC > 8 years	18
Primary sclerosing cholangitis	6
Backwash ileitis	2

Among the 15 patients who underwent biopsy at 10- to 12-cm intervals, flat dysplasia was detected in 60% (9/15) and CAC in 67% (10/15) during preoperative colonoscopy, whereas in the other 9 patients the rate of flat dysplasia was 33% (3/9) and of CAC 56% (5/9). Despite regular surveillance (once a year, one to four biopsy specimens obtained at approximately 10-cm intervals), nine of our patients developed invasive carcinoma without any dysplastic lesions detected by prior colonoscopy. In this group, however, flat dysplasia was diagnosed in six of nine (67%) patients by preoperative colonoscopy. In two of these patients CAC was still missed by preoperative colonoscopy.

A total of 36 tumors were identified in 24 resected specimens, almost 50% of which were located in the rectum. Tumor stages of the patients are summarized in Table 2 [27]. Additional flat dysplasia was found in 15 (62.5%) resected specimens: 8 of them had high grade dysplasia, and 7 had both high and low grade dysplasia.

Most of the patients had additional risk factors for cancer, the most common of which were long-standing UC (> 8 years) and pancolitis (Table 3). Most patients had at least two additional cancer risk factors; five patients had three additional risk factors. The following cancer risk factors were observed in six patients with UC duration < 8 years: therapy-refractory UC (n = 6), pancolitis (n = 6), primary sclerosing cholangitis (n = 3), backwash ileitis (n = 1), early onset of UC (n = 2).

Discussion

It is generally recognized that there is an increased risk of CAC in patients with UC [1–4, 21–23, 28]. This threat is particularly high in patients with certain risk factors. For these patients, mucosal dysplasia obtained by surveillance colonoscopy is used as a marker for the subsequent development of colorectal cancer. However, much controversy exists about the importance and efficacy of this proceeding [1, 18–20].

In several studies there was high interobserver variation among pathologists when grading dysplasia in UC patients [19, 29, 30]. In particular, the observers disagreed about low grade dysplasia just as much as reactive hyperplasia and cellular atypia. Epithelial dysplasia is difficult to recognize by colonoscopy because of its appearance in flat areas [19, 29–31]. Furthermore, many UC patients develop CAC in the absence of dysplasia [28, 29].

This was confirmed by our study, where we found preoperatively diagnosed flat dysplasia in only 50% (12/24) of patients with CAC. In a recent study, 68% of patients with CAC did not have a preoperative diagnosis of dysplasia [32]; Shelton et al. [33] reported similar findings, with preoperative dysplasia present in only a small number of CAC patients (32%). This is certainly at least in part attributable to inadequate surveillance, as confirmed by our study, where only 14 of 24 patients had had their last colonoscopy for surveillance during the 2 years before cancer diagnosis; moreover, random biopsy specimens were obtained at approximately 10-cm intervals in only 15 of 24 patients. This is a common problem with all surveillance programs and should give us a realistic picture of the limitations of any such program.

Connell et al. [26] found an increased rate of UC patients who developed CAC if colonoscopy was performed only every second year compared to patients in whom colonoscopy was done each year. Moreover, it has been estimated that 33 to 56 biopsy specimens are required to be 90% to 95% confident of detecting dysplasia [34]. In our study patients with biopsy specimens obtained at approximately 10-cm intervals showed synchronous flat dysplasia more frequently than did patients without this rigorous approach. However, even in this patient group some flat dysplasia could have been missed because of the variability in the number of biopsy specimens per site. Conversely, in a study of colectomy specimens from patients with UC, Taylor et al. [35] found that 26% of those with cancer had no dysplasia, confirming our results that a significant number of patients develop cancer without any evidence of dysplasia. In this regard, it is of particular interest that despite regular surveillance nine of our patients developed invasive carcinoma without any dysplastic lesions detected by prior colonoscopy. It is not clear why in only 63% of patients carcinoma was diagnosed preoperatively by colonoscopy in our study, as other investigators have found CAC preoperatively in 78% to 92% of patients [32, 36, 37].

A review of prospective surveillance studies in patients with UC by Bernstein et al. [1] analyzed 10 studies that included 1225 patients. They found that a significant number of patients with DALM or high grade dysplasia had cancer at the time of colectomy, as confirmed by our results. Moreover, some of the patients with low grade dysplasia who underwent immediate colectomy already had cancer, indicating that surveillance colonoscopy is of dubious benefit.

Surveillance colonoscopy is recommended every 1 to 2 years, beginning 8 years after the start of pancolitis and 12 to 15 years after the start of left-side colitis [38, 39]. Our data suggest that when using the colonoscopic approach some UC-associated cancers are missed: 25% of our patients had documented UC within 8 years of diagnosis (but all of them had several cancer risk factors) and would not have been included in the surveillance program. Similar results were described by Mayer et al. [32], where 18% of patients had a UC history for less than 8 years before the development of carcinoma.

In addition to long disease duration, extent of the inflammation, and established cancer risk factors, PSC and early onset of the disease were discussed as further risk factors influencing the frequency of CAC [13–16, 28, 40–43]. Age has been demonstrated to be an independent clinical risk factor in most studies, and the risk of CAC is believed to be significantly greater if the onset of UC is before the age of 15 years [6, 20]. In our study most of the patients had pancolitis, approximately 20% of patients were younger than 20 years when the UC diagnosis was established, and 25% of patients had PSC.

Heuschen et al. [44] found CAC in 5% of patients with a UC duration of less than 10 years, with an increased risk for patients older than 45 years at the time of the UC diagnosis. This was confirmed by our results, where four of six patients with a UC duration of less than 8 years were older than 45 years at the time of the UC diagnosis, and all of our patients with a short UC duration had several cancer risk factors. Interestingly, similar findings were described recently for Crohn's colitis [45], assuming that not only patients with early onset of inflammatory bowel diseases are at increased cancer risk but also patients with short-duration disease who are more than 45 years of age. Heuschen et al. [44] found an increased frequency of CAC in UC patients with backwash ileitis. In our study only two patients had mucosal inflammation of the terminal ileum.

We recognize that our retrospective, nonrandomized study inevitably introduces a selection bias. We also recognize that a prospective study with defined surveillance protocols could have increased the number of dysplastic lesions. However, many failures of surveillance are reported even from specialty centers [1, 19]. It is also impossible for us to determine the relative importance of several potential factors that could lead to surveillance failure. The most likely reasons for our patients who had had their last colonoscopy more than 2 years before cancer detection are ignorance of their cancer risk and nonreferral of appropriate patients by physicians.

Conclusions

Our study showed that colonoscopic surveillance for dysplasia is not as promising as expected in a significant number of patients. Therefore in patients with significant cancer risk factors, monitoring should be intensified; moreover, in addition to the standard histologic examination of the retrieved mucosal biopsy specimens, screening for some of the promising molecular markers should be undertaken [46, 47]. It must be made clear to these patients that surveillance by colonoscopy is associated with a significant rate of histologic error. Information should also always include surgical options for definitive treatment of UC and, thereby, prevention of CAC in a subset of UC patients with significant cancer risk factors.

Résumé. Les patients porteurs d'une rectocolite hémorragique (RCH) ont plus de risques de développer un cancer colorectal (CCR). Malgré un suivi par coloscopie de près chez les patients à risque élevé, afin de détecter une dysplasie, la prévalence de CCR est toujours irrecevablement haute. Le but de cette étude a été d'évaluer la prévalence des facteurs de risque du CCR, tel la dysplasie, et de déterminer l'importance de la surveillance coloscopique dans le groupe de patients qui ont éventuellement développé un CRC. 24 patients ayant une RCH ont développé un CCR. Les dossiers de ces patients ont été analysés de façon rétrospective, pour étudier la durée de la RCH, la prévalence de dysplasie préopératoire et d'autres facteurs de risque pour le cancer (par ex: la pancolite, la cholangite sclérosante primitive (CSP), un début précoce de RCH et l'iléite dite «de reflux»). L'âge moyen des patients au moment du diagnostic du CCR a été de 43 ans après une durée moyenne de la maladie de 15 ans (6 patients avaient une RCH moins de 8 ans). Le CCR a été identifié en préopératoire par coloscopie chez 15 des 24 patients, avec 7 sur 15 montrant une dysplasie de type «plane». Cinq de neuf patients sans CCR diagnostiqué en préopératoire avaient une dysplasie de type "plane." Au total, 19 patients avaient un facteur de risque supplémentaire, la plupart ayant au moins deux autres facteurs de risque. Malgré une surveillance régulière par coloscopie pour la plupart de patients ayant une RCH, la dysplasie de type «plane» est passée inaperçue chez 12 patients en préopératoire. Ainsi nous suggérons que

l'information au patient doit toujours inclure toutes les options chirurgicales possibles dans chaque cas où des risques significatifs de CCR sont retrouvés.

Resumen. Los pacientes con colitis ulcerativa (CU) tienen un riesgo aumentado de desarrollar carcinoma colo-rectal (CCR). A pesar de que estos pacientes en riesgo son seguidos con colonoscopia destinada a identificar displasia, la prevalencia de CCR todavía es inaceptablemente elevada. El propósito del presente estudio fue evaluar la prevalencia de factores de riesgo de CCR, tales como displasia, y determinar la pertinencia del seguimiento colonoscópico en el grupo que desarrolló cáncer. En veinticuatro pacientes con CU se estableció el diagnóstico de CCR. Se analizaron sus historias clínicas en forma retrospectiva en cuanto a la evolución de la CU, la prevalencia de displasia preoperatoria y otros factores de riesgo de cáncer (FRC) (ej. pancolitis, colangitis esclerosante primaria, comienzo precoz de la CU e ileitis). La edad promedio de los pacientes en el momento del diagnóstico fue 43 años, con una evolución promedio de la CU de 15 años (6 tuvieron CU < 8 años). El CCR fue identificado preoperatoriamente por colonoscopia en 15 de los 24 pacientes, y 7 pacientes adicionales entre 15 mostraron displasia plana. Cinco de 9 sin el diagnóstico preoperatorio del CCR tenían displasia plana. En total 19 pacientes tenían FRC adicionales, la mayoría con no menos de 2. A pesar de un seguimiento colonoscópico regular en la mayoría de los pacientes con CU, la displasia plana pasó inadvertida en 12 casos preoperatorios. Por consiguiente, nuestra sugerencia es que en la información que se provea al paciente siempre se incluyan las opciones quirúrgicas en todo caso en que se identifiquen FRC significantes.

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