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ORIGINAL ARTICLE

The Risk of Colorectal Cancer in Patients with Ulcerative Colitis

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Abstract
Background and Aim Ulcerative colitis increases the risk of developing dysplasia and colitis-associated cancer (CAC). The purpose of this study was to determine the risk factors as well as protective measures for disease burden, need for colectomy and the development of CAC in ulcerative colitis (UC) patients.
Methods A cohort of $n = 434$ UC patients was evaluated. Data analysis was performed by univariate and multivariate logistic regression. Odds ratios (OR) and 95 % confidence intervals (CI) were calculated, and significance was assessed by the likelihood ratio test.
Results Mean patient age at UC diagnosis was 45.7 ± 15.1 years which manifested mainly as pancolitis (47 %) or left-sided colitis (45.2 %). CAC was detected in ten patients (2.3 %). UC disease duration was strongly associated with the risk of CAC ($P < 0.0014$); disease duration between 9 and 15 years: OR of 2.5 (95 % CI 0.2–41.1), more than 15 years: OR of 21.4 (95 % CI 2.6–173.6). The risk of developing dysplasia (low-grade intraepithelial neoplasia, LGIEN and high-grade intraepithelial neoplasia, HGIEN) or the need to undergo colectomy was also significantly related to disease duration ($P = 0.006$, $P = 0.002$, respectively). Established anti-inflammatory medication (e.g., 5-ASA, anti-TNF-α) significantly reduced the risk of both dysplasia and CAC ($P = 0.02$).
Conclusions Despite the use of modern therapies for UC, CAC rates remain high. In our study, risk factors included disease duration while anti-inflammatory therapies reduced the risk. Effective control of the intestinal inflammation also reduced the disease burden as indicated by decreased risk of requiring colectomy, underscoring the need for sufficient surveillance and anti-inflammatory therapies.

Tobias M. Nowacki, Markus Brückner, Matthias Ross and Dominik Bettenworth have contributed equally to this work.

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Keywords Inflammatory bowel disease (IBD) · Ulcerative colitis (UC) · Colitis-associated cancer (CAC) · Colorectal cancer · Surveillance

Introduction

Chronic colonic inflammation is a well-known risk factor for the development of colorectal malignancy [1]. Patients with ulcerative colitis (UC) are at particularly increased risk of developing colitis-associated cancer (CAC) [2, 3]. While the incidence of sporadic colorectal cancer (CRC) is increased from the fifth decade of life, and maximal in the eighth decade, the median age of CAC diagnosis is 43 years [4, 5]. CAC has a significant impact on UC patients, with cause-specific mortality due to CRC significantly higher in UC patients compared to the background population. Munkholm et al. [6] demonstrated 15 % of all deaths in UC patients to be a consequence of CRC. Validated risk factors for CAC are helpful to stratify the individual patients' risk and include severity and duration of disease, primary sclerosing cholangitis (PSC) as well as a positive family history for CRC [7–11].

Historically, the risk of CAC was first reported in a pediatric cohort. Devrode et al. [12] found the risk to be 20 % per decade beginning 10 years after diagnosis. More recently, a large meta-analysis including 116 studies revealed incidence rates corresponding to cumulative probabilities of 2 % by 10 years, 8 % by 20 years and 18 % by 30 years of disease duration [8]. In the same study, the overall prevalence of CRC was reported to be 3.7 % (95 % CI 3.2–4.2 %). In contrast, a recent study from Denmark found no increased incidence of CAC and was confirmed by another study including 32,991 UC patients that found no increase in CAC over a 30-year period [13, 14]. In accordance with these findings, a more recent meta-analysis by Jess et al. [15] only found CAC occurring in 1.6 % of UC patients within 14 years of diagnosis which is significantly less compared to the studies described earlier [8].

Endoscopic surveillance programs for detection of precancerous dysplasia have been evaluated for IBD patients and been proven to facilitate a reduced colorectal carcinoma-related mortality rate [16, 17]. Current guidelines recommend to begin screening colonoscopy, including random biopsies every 10 cm of bowel, in UC patients with more than one-third of the colon involved 8–10 years after initial diagnosis [18]. Subsequently, colonoscopy is suggested every 1–2 years in UC patients, and annually in patients diagnosed with PSC. However, even when screening complies with guidelines, CAC diagnosis is delayed or missed in 18–27 % of UC patients [19, 20], a problem compounded by low patient uptake of surveillance programs offered to those with long-standing extensive colitis [21].

Repetitive colonic inflammation not only fuels the disease burden for the individual patient but also increases the risk to require colectomy and colectomy-free survival rates have been proposed as a measurement of therapeutic effectiveness [22]. Yet, risk factors for the need for colectomy are not well established.

The aim of the present study was to evaluate risk factors for colectomy, development of dysplasia (LGIEN, HGIEN) and colon cancer, as well as to determine protective measures in a relatively large cohort of UC patients at a tertiary referral center.

Methods

Enrollment of Patients and Data Collection

We retrospectively analyzed 434 patients treated as inpatients or outpatients between 2002 and 2013 at the Department of Gastroenterology, University Hospital of Münster, a tertiary referral center for IBD patients in northwestern Germany. Patients with UC as principle diagnosis were identified by searching for code K51 (International Classification of Diseases, version 10, ICD-10). Additionally, patients with both UC and colorectal cancer were identified by search for codes C18; C19; and C20. Diagnosis of UC was based on clinical presentation, exclusion of infectious enteritis and colitis as well as endoscopic and histopathological findings. Data on demographics (age and sex), disease characteristics including duration (time elapsed since initial diagnosis), disease severity (assessed by Mayo score) and manifestations (location and extent of disease (determined as the maximal extent of colonic involvement: proctitis, left-sided colitis or pancolitis according to the Montreal classification [23])) were collected from patient's clinical records (shown in Tables 1, 2) in a cross-sectional analysis. Additionally, data on colitis-related proctocolectomy, presence and grade of any dysplasia and CAC, as well as colitis-related specific anti-inflammatory and immunosuppressive medication were collected.

Of 455 patients, 21 patients (5.2 %) were excluded from our analysis due to insufficient data being available; leaving a total 434 patients included. Of these patients, any with missing or unavailable data within a single category led to exclusion of that patient from that specific analysis only, rather than from the study.

Table 1 Demographic and clinical data of patients with UC as principle diagnosis ($n = 434$)

Mean age ± SD	45.7 ± 15.1
Males/females	255 (58.8)/179 (41.2)
Max. extent of disease	
Proctitis	27 (7.8)
Proctosigmoiditis/colitis of left colon	156 (45.2)
Pancolitis	162 (47)
Duration of disease	
Initial diagnosis	23 (6)
1–8 years	189 (49.3)
9–15 years	84 (21.9)
>15 years	87 (22.7)
Mayo score	
0–3	136 (44.2)
4–6	51 (16.6)
7–9	61 (19.8)
10–12	60 (19.5)
Presentation of dysplasia	
No dysplasia detected	322 (92.3)
Low-grade intraepithelial neoplasia (LGIEN)	12 (3.4)
High-grade intraepithelial neoplasia (HGIEN)	5 (1.4)
Invasive colon carcinoma	10 (2.3)
Colitis-associated colectomy	
Yes	74 (17.4)
No	352 (82.6)
Extraintestinal manifestation	
No extraintestinal manifestation	322 (80.5)
Arthropathy	40 (10)
Erythema nodosum	5 (1.3)
Primary sclerosing cholangitis	31 (7.8)
Uveitis	2 (0.5)

Values are given as total numbers with valid percentages in parentheses unless stated otherwise

Table 2 Demographic and clinical data of patients with CAC ($n = 10$)

Mean age ± SD	54.7 ± 17.3
Males/females	5/5
Max. extent of disease	
Proctitis	0
Proctosigmoiditis/colitis of left colon	4
Pancolitis	6
Duration of disease	
Initial diagnosis	0
1–8 years	1
9–15 years	1
>15 years	8
Mayo score	
0–3	4
4–6	1
7–9	–
10–12	2
Unknown	3
Presentation of dysplasia	
No dysplasia detected	0
Low-grade intraepithelial neoplasia (LGIEN)	0
High-grade intraepithelial neoplasia (HGIEN)	0
Invasive colon carcinoma	10
Proctocolectomy	
Yes	10
No	0
Extraintestinal manifestation	
No extraintestinal manifestation	6
Arthropathy	1
Erythema nodosum	0
Primary sclerosing cholangitis	3
Uveitis	0
Death	
Yes	2
No	8

Values are given as total numbers unless stated otherwise

Assessment of Disease Activity and Histological Analysis

Severity of disease was assessed clinically and endoscopically using the Mayo scoring system as described elsewhere [24]. Briefly, Mayo scoring was performed using the following criteria: stool frequency, rectal bleeding, endoscopic findings and physician's global assessment. Data from colonoscopic surveillance were available for 380 patients (87.6 %). For patients without current endoscopy results, a partial Mayo score was assessed as follows: stool frequency, rectal bleeding and physician's global assessment. Clinical severity of UC was assessed from the most recent available patient visit (cross-sectional analysis) or from the visit at detection of any dysplasia, respectively. The extend of disease was determined as the maximal endoscopically recorded disease extend. Histological analysis of biopsy specimens was performed routinely by pathologists as per the IBD Dysplasia Morphology Study Group [25]. In cases of invasive carcinoma, biopsies were sent to a second expert pathologist to confirm diagnosis. Specimens were classified as either negative for dysplasia, low-grade intra-epithelial neoplasia (LGIEN), high-grade intraepithelial neoplasia (HGIEN) or CAC. The histological degree of inflammation was not routinely outlined in all pathologic reports.

Statistical Analysis

Mean, standard deviation (SD), range and proportions were calculated to analyze patients' baseline characteristics. The probability of CAC, dysplasia and colectomy was modeled using univariable binary, univariable multinomial and multivariate logistic regression to assess different severities of neoplasia. Odds ratios (OR), corresponding 95 % confidence intervals (95 % CI), likelihood ratio-type P values for the binary logistic regression and for the multinomial logistic regression were calculated. In a second step, multivariate logistic regression analysis with stepwise forward selection of variables was performed; parameters with P values ≤ 0.05 in the likelihood ratio test were included in the model. Inferential statistics are intended to be exploratory, not confirmatory, and were interpreted accordingly. The comparison-wise type-I error rate is controlled instead of the experiment-wise error rate. The significance level was set at $P < 0.05$. No adjustment for multiple testing was performed. Statistical analyses were performed using IBM SPSS® Statistics 21 for Windows (IBM Corporation, Somers, NY, USA) and R 2.15.3 (R Development Core Team, 2011; R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients' Characteristics

Mean age at presentation was 45.7 ± 15.1 years and ranged from 20 to 97 years. The male-to-female ratio was 1.4:1 with 58.8 % male patients. Demographic data are summarized in Table 1. A total of 49.3 % had a disease duration of 1–8 years; 21.9 % of the patients had UC diagnosed for 9–15 years, and 22.7 % longer than 15 years. With regard to disease extension, only 7.8 % of patients were diagnosed with ulcerative proctitis, whereas 45.2 % were diagnosed with left-sided colitis and 47 % with pancolitis. A complete Mayo score could be assessed in 308 (71 %) patients, and 44.2 % of these patients scored between 0 and 3, reflecting mild disease activity, 16.6 % scored between 4 and 6, while 19.8 % scored 7–9, and 19.5 % scored 10–12 points. Colectomy was performed in 17.4 % of patients due to refractory disease or detected colonic dysplasia, while 352 patients (82.6 %) were treated conservatively. In addition, 78 patients (19.5 %) showed additional extraintestinal manifestations of UC including arthralgia (10 %) and PSC (7.8 %).

The most frequently administered anti-inflammatory and/or immunosuppressive medication was mesalazine (18.3 %), mesalazine with oral prednisolone (13.3 %) or mesalazine plus azathioprine (9.8 %). In total, 56.6 % of UC patients received 5-aminosalicylic acid (5-ASA) medication either alone or in combination with other anti-inflammatory drugs. A total of 14.7 % of patients did not receive any anti-inflammatory medication. Between 2002 and 2013, eight patients (1.8 %) were newly diagnosed with CAC, while two additional patients had been diagnosed prior to 2002. Mean age was 54.7 ± 17.3 years, and the male-to-female ratio was 1:1. Eight patients with CAC suffered from UC longer than 15 years, one patient between 9 and 15 years and one patient between 1 and 9 years. The disease extent was as follows: six patients showed a pancolitis and four patients a left-sided colitis. After histological confirmation of invasive carcinoma by a second pathologist, all patients underwent proctocolectomy. Subsequently, four patients received adjuvant chemotherapy; one patient was treated with supportive care due to poor general condition; and in five patients, further treatment was not indicated according to current treatment guidelines. Two patient deaths occurred, one due to cholangiosepsis secondary to biliary obstruction resulting from a coincident Klatskin tumor. No other malignancies were observed in the patients with CAC. Further clinical characteristics of patients with CAC are shown in Table 2.

Need for Colitis-Related Colectomy

In our cohort of 434 patients, 74 patients (17.4 %) underwent colectomy. These patients were generally older (mean age 49.4 ± 14.6 vs. 44.7 ± 15.2 years) and had a longer disease duration and more extensive colonic involvement compared to non-colectomized patients (Fig. 1). No correlation could be detected for patient gender. Patients with disease duration of more than 15 years had a significantly greater risk to undergo colectomy compared to patients in the first 8 years of the disease (OR 2.4; 95 % CI 1.3–4.2; $P = 0.005$). According to the Montreal classification, the extent of disease was clearly associated with the need for colectomy in our cohort. The risk of colectomy was highest in patients with pancolitis (OR 2.9; 95 % CI 1.6–5.5; $P = 0.001$) while anti-inflammatory or immunosuppressive treatment significantly reduced the risk of colectomy (OR 0.2; 95 % CI 0.1–0.4; $P < 0.001$). Particularly, patients treated with mesalazine had a markedly lower risk of requiring colectomy as compared to those without therapy (OR 0.2; 95 % CI 0.1–0.4; $P < 0.001$). This was also true when adjusted for disease severity reflected by partial Mayo score. In the multivariate logistic regression analysis, treatment with 5-ASA was found to be an independent protective factor. Furthermore, the risk to require colectomy increased with an elevated partial Mayo score (data not shown). Medical treatment with thiopurines also reduced the risk of requiring colectomy (OR 0.3; 95 % CI

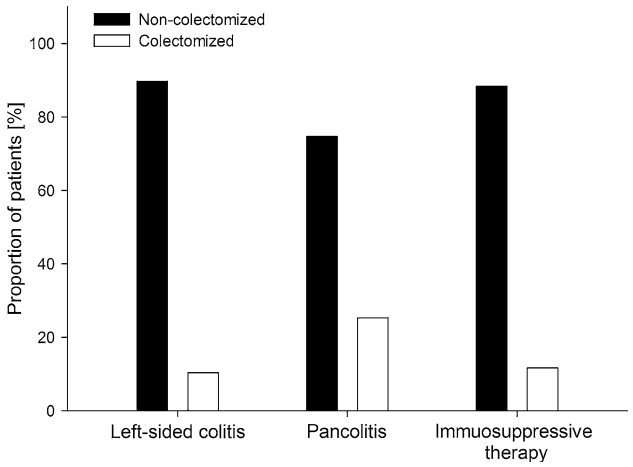

Fig. 1 Frequency of colectomy is highest in patients with pancolitis. Data analyzed by stepwise forward logistic regression for colectomized and non-colectomized patients are depicted with regard to extent of disease (left-sided colitis and pancolitis) and immunosuppressive therapy. Shown are percentages of patients applicable for each category

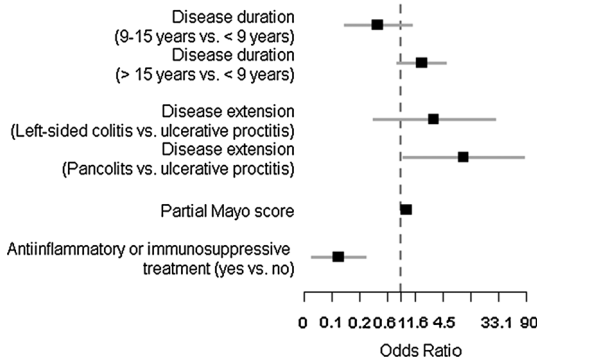

Fig. 2 The risk to require colectomy is increased in more extensive and greater duration of disease, while anti-inflammatory treatment is protective. Multinomial logistic regression was applied to calculate odds ratios (with 95 % CI) for several risk factors for patients to require colectomy. While anti-inflammatory treatment proved to be protective, a longer disease duration (more than 15 years vs. the first 8 years of disease) and more extensive disease (pancolitis vs. proctitis) increased the risk significantly

0.1–0.8; $P = 0.01$), whereas treatment with anti-TNF antibodies did not show significant effects (OR 0.8; 95 % CI 0.2–2.7; $P = 0.659$).

Additionally, we employed multivariate logistic regression analysis with stepwise forward selection of variables to identify protective as well as risk factors for colectomy. In support of our previous observations, this model identified greater disease severity (partial Mayo score OR 1.2; 95 % CI 1.1–1.4; $P = 0.001$) as well as more extensive disease (left-sided colitis OR 3.3; 95 % CI 0.4–28.4; pancolitis OR 9.3; 95 % CI 1.1–79.0; $P = 0.003$) and a longer duration of disease (duration > 15 years OR 2.1; 95 % CI 0.9–5.0; $P = 0.032$) to increase the risk of colectomy. In contrast, any pharmaceutical therapy (OR 0.1; 95 % CI 0.0–0.3; $P < 0.01$) or a shorter duration of disease (duration 9–15 years OR 0.4; 95 % CI 0.1–1.4) decreased the risk of colectomy (Fig. 2).

Prevalence of Dysplasia (LGIEN/HGIEN)

Dysplasia (LGIEN and/or HGIEN) was detected in 17 patients, while invasive carcinoma was detected in 10 out of 349 patients during screening colonoscopy. A total of 48.1 % of affected patients (13 of 27) had a disease duration of more than 15 years (Fig. 3), and binary logistic regression revealed that disease duration was significantly associated with an increased risk to develop dysplasia. There was an increased chance to develop dysplasia nine years after diagnosis (OR 1.6; 95 % CI 0.5–4.8) and after more than 15 years (OR 4.3; 95 % CI 1.8–10.5) as compared to patients with a disease duration of <8 years

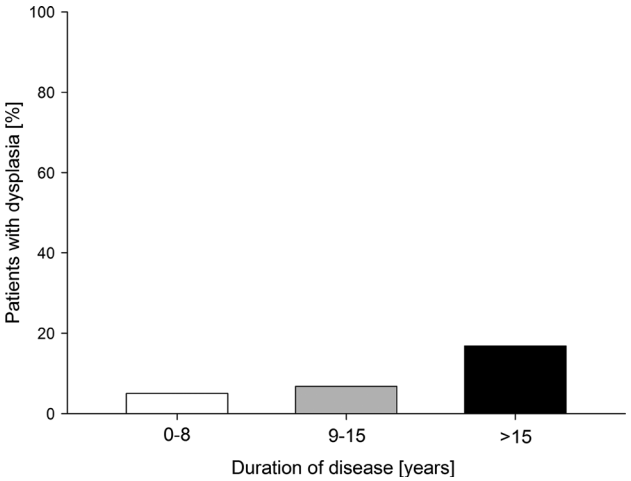

Fig. 3 The frequency of dysplasia development increases with longer disease duration. Dysplasia and invasive carcinoma were detected in 27 out of 349 (7.7 %) patients during screening colonoscopy. Shown are percentages of patients with dysplastic lesions (LGIEN and/or HGIEN) stratified according to disease duration, indicating a significant association of dysplasia development and disease duration

($P = 0.006$). In accordance with the binary logistic regression analysis, multinomial regression revealed a significant association of disease duration with the development of dysplasia and consecutive carcinoma. In comparison with patients with CAC, all other UC patients had a 23.8 times higher chance of remaining without dysplasia in the first 8 years after diagnosis (OR 23.8; 95 % CI 2.9–193.6; $P < 0.01$) and a 8.5 times higher chance after 9–15 years of disease (OR 8.5; 95 % CI 1–69.9; $P < 0.01$). Furthermore, the risk of UC patients without CAC to

"merely" develop LGIEN was tenfold higher in the first 8 years (OR 10.0; 95 % CI 0.9–117.0) and sixfold higher after 9–15 years of disease (OR 6.0; 95 % CI 0.5–77.8).

There was no significant relationship between the development of dysplasia and the extent of disease ($P = 0.405$). However, a clear tendency toward an increased number of dysplastic lesions was documented in case of extended colonic involvement compared to patients suffering from proctitis: left-sided colitis (OR 2.0) versus pancolitis (OR 2.9). The risk to develop dysplasia significantly increased after 10 years of disease (OR 1.4; 95 % CI 1.1–1.8; $P = 0.004$). In contrast, sex or partial Mayo score did not show an association with the development of dysplasia.

As chemoprotective effects of therapeutic drugs are reported [26], the impact of anti-inflammatory and/or immunosuppressive medication on CAC development was assessed. Of note, anti-inflammatory/immunosuppressive therapy significantly reduced the risk of dysplasia development (OR 0.4; 95 % CI 0.2–0.8; $P = 0.022$). These results were confirmed by multinomial regression analysis showing a 4.2 times higher chance for patients without medical therapy to develop dysplasia or invasive carcinoma (OR 4.2; 95 % CI 1.2–15.6). Finally, in a process of variable selection, a multivariable model identified the variables "age (per 10 years)" (OR 1.3; 95 % CI 1.0–1.8; $P = 0.092$) and "anti-inflammatory and/or immunosuppressive therapy" (OR 0.3; 95 % CI 0.1–0.8; $P = 0.026$), duration of disease (duration 9–15 years OR 1.6; 95 % CI 0.5–5.4; duration > 15 years OR 2.7; 95 % CI 0.9–7.8; $P = 0.19$) and severity of disease (Partial Mayo score OR 1.04; 95 % CI 0.9–1.2; $P = 0.555$) to explain the development of dysplasia best (Fig. 4).

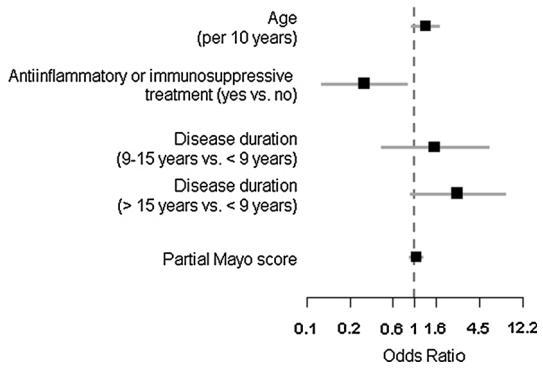

Fig. 4 The risk to develop dysplasia is increased by longer disease duration, while anti-inflammatory treatment is protective. Stepwise forward logistic regression was applied to calculate odds ratios (with 95 % CI) for several risk factors for patients to develop dysplasia. While anti-inflammatory treatment proved to be protective, duration of disease (duration 9–15 years OR 1.6; 95 % CI 0.5–5.4; duration > 15 years OR 2.7; 95 % CI 0.9–7.8; $P = 0.19$) and severity of disease (Partial Mayo score OR 1.04; 95 % CI 0.9–1.2; $P = 0.555$) were identified as independent risk factors for the development of dysplasia

Carcinoma

Eight patients (1.8 %) were newly diagnosed with CAC between 2002 and 2013, while two additional patients of the analyzed cohort had been diagnosed with CAC prior to 2002. Histological analysis proved all tumors were adenocarcinomas. Three patients with CAC showed PSC as extraintestinal manifestation of UC, underscoring its role as a risk factor for carcinoma development in this study (OR 5.6; 95 % CI 1.3–23.7). On the other hand, logistic regression did not reveal extraintestinal manifestation in general to be a significant risk factor for the development of CAC ($P = 0.439$). At the time of cancer diagnosis, tumor manifestation was categorized as UICC (Union internationale contre le cancer) stage IIa in five patients, stage IIIa in two patients and stage IV in one patient. Duration of disease significantly increased the risk to develop colon carcinoma. In detail, the chance of CAC development after 9–15 years of disease was significantly increased as compared to the first 8 years of disease (OR 2.5; 95 % CI 0.2–41.1). In contrast, disease duration of more than 15 years highly increased the chance by a factor 21 (OR 21.4; 95 % CI 2.6–173.6; $P < 0.001$). In accordance with our observation regarding dysplasia development, no significant relationship was found between the development of CAC and the extent of disease ($P = 0.37$, Fig. 5). Anti-inflammatory and/or immunosuppressive treatment significantly reduced the chance to develop CAC (OR 0.3; 95 % CI 0.1–1.0), whereas no significant effect could be observed by a single medication like 5-ASA (OR 0.9; 95 % CI 0.2–3.6; $P = 0.912$), thiopurines (OR 0.7; 95 % CI 0.1–3.3; $P = 0.603$) or anti-TNF (OR 1.6; 95 % CI 0.2–13.8; $P = 0.675$). In the univariate analysis, no significant relation was found between development of CAC and the severity of disease as reflected by partial Mayo score ($P = 0.82$), as well as gender ($P = 0.57$). The variable "age" tended to have an influence ($P = 0.07$) with an OR of 1.04 (95 % CI 1.0–1.1) meaning that a difference of 10 years of age increased the chance for carcinoma about 42 %. Interestingly, patients receiving medical therapy including anti-TNF antibodies tend to have a slightly increased risk for carcinoma development, although not reaching statistical significance (OR 1.6; 95 % CI 0.2–13.8; $P = 0.69$) and probably being confounded by the factor severity of disease represented by Partial Mayo score: Patients with mesalazine as single therapy were categorized with an average score of one, whereas patients treated with anti-TNF antibodies had an average score of four points. Finally, a variable selection generated a final multivariable model choosing the

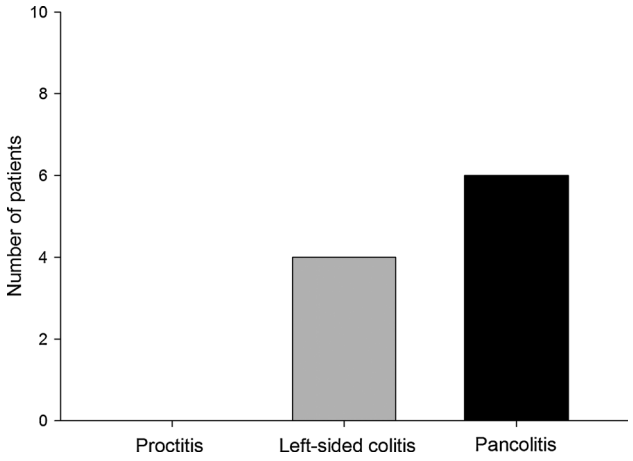

Fig. 5 Development of CAC occurs mainly in patients with more extensive disease. Ten patients out of 434 were diagnosed with CAC. Depicted is the total number of patients for the respective extent of disease specified on the x-axis

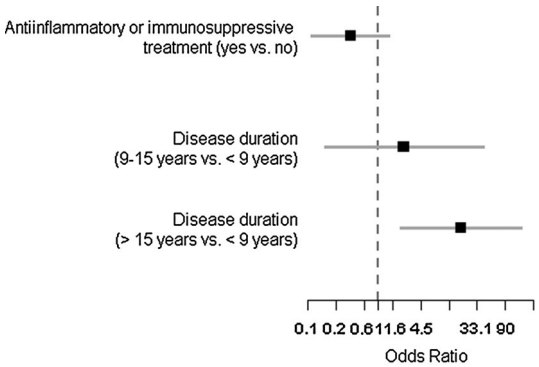

Fig. 6 The risk to develop CAC is increased by longer disease duration, while anti-inflammatory treatment is protective. Stepwise forward logistic regression was applied to calculate odds ratios (with 95 % CI) for several risk factors for patients to develop CAC. While anti-inflammatory treatment proved to be protective, duration of disease was identified as an independent risk factor for the development of CAC

variables "anti-inflammatory and/or immunosuppressive therapy" (OR 0.4; 95 % CI 0.1–1.5; $P = 0.170$), "duration of disease 9–15 years" (OR 2.5; 95 % CI 0.2–40.1) and "duration of disease of more than 15 years" (OR 18.8; 95 % CI 2.3–155.0; $P = 0.001$) to explain the development of CAC best (Fig. 6).

Discussion

In this study, we documented ten newly diagnosed cases of CAC in our cohort of 434 UC patients. In accordance with established risk factors, we found duration of UC to be strongly associated with the highest risk of cancer development in our single-center experience. In addition, our data show that anti-inflammatory medication use can decrease the risk of CAC development. Existing epidemiological data on the incidence rate of CAC in UC patients are conflicting. While historic data hint at markedly increased rates (3.7 %), other studies found comparable risk rates or only slightly increased rates of 1.6 or 1.7 % [8, 15, 27]. Although direct comparisons of crude colorectal cancer occurrence rates and incidence ratios in our study and population-based studies are not possible, the observed occurrence rate of 1.8 % tends toward the more recent reported incidence rates [15]. Despite the limitations of this study in determining incidence rates, the observed occurrence rates for CAC were still lower than initially reported incidence ratios [8] although our hospital is a tertiary referral center for IBD patients. This could be explained by either methodological aspects (retrospective hospital-based vs. population-based studies, heterogeneous follow-up periods) or truly decreased risk factors due to improved (therapeutic) disease control and surveillance with increased rates of colectomy.

Approximately 20 % of UC patients will require surgical treatment and interestingly, and recent studies document that the introduction of immunosuppressive therapy did not change colectomy rates over time [28]. This finding is in line with the colectomy rates of ~17 % in our cohort. We found a significant association between severity and duration of disease and the risk to require colectomy. Additionally, effective control of the colonic inflammation was demonstrated to be a protective effect both, on the risk to develop CAC, dysplasia and to require colectomy. One might postulate that indeed more effective anti-inflammatory therapies and the consistently high rates of colectomy contribute to the recently observed reduced risk to develop CAC. Considering colectomy-free survival as one aspect of intestinal damage, our study identified several risk factors including severity, extent and duration of disease, while anti-inflammatory therapy significantly reduced the risk. Accordingly, these aspects of disease behavior may be used for individual risk stratification and to detect severe courses of disease and additionally underscore the need for tight control of the colonic inflammation.

We found a strong association between the duration of UC and the prevalence of CAC. As compared to the risk of cancer development in the first 8 years after diagnosis, the risk significantly increased between 9 and 15 years and was even higher after 15 years of disease. Although a British cohort surveillance report found no increased carcinoma rates with increasing disease duration [29], this observation confirms previously reported disease duration as a main risk factor for colorectal malignancy [8].

In the light of recent molecular insights into the tumor development, the relation between long-lasting colonic inflammation and the genesis of CAC seems particularly reasonable. Several studies demonstrate the link between the development of CAC in UC with chronic inflammation inducing genomic alterations, e.g., through executors of oxidative stress such as reactive oxygen and nitrogen species causing microsatellite instability and impairment of DNA repair processes [30, 31]. However, more recently, direct effects of the inflammation itself on tumor development were revealed. For example, the pro-inflammatory cytokine interleukin-6 (IL-6) has an impact on the pathogenesis of CAC. It was shown that UC patients with active flare of disease had significantly more IL-6-positive intestinal epithelial cells as compared to those patients with quiescent disease. Functionally, it may be hypothesized that long-term inflammatory changes in these patients multiply inflammation-induced premalignant alterations ultimately leading to the development of CAC.

Interestingly, in our patient cohort, we did not find a significant correlation between the development of dysplasia and/or CAC and the extent of disease or severity of disease. These findings may have been influenced by different definitions of disease extension (either endoscopic or histological), the cross-sectional nature of disease severity analysis and by the fact that IBD-related and sporadic neoplasia were cumulatively evaluated in the present analysis without histological classification of the degree of inflammation. However, the association of inflammatory severity and the risk to develop dysplasia is well established [32], and in our study, there was a clear tendency of increased risk of dysplasia in case of extended colonic involvement as compared to proctitis: left-sided colitis (OR 2.0) and pancolitis (OR 2.9). Vice versa, proctitis and proctosigmoiditis did not increase the risk of CAC [33], and confirmatively, none of our carcinoma patients suffered from proctitis or proctosigmoiditis. In addition, PSC as another established risk factor for CAC was present in three of ten (30 %) patients, but not reaching a significant association. Nevertheless, taken into account that data from 434 UC patients were analyzed, we hypothesize that larger cohorts might confirm the role of extensive disease and PSC as independent risk factors.

Due to the abundant evidence in the literature proving that chronic inflammation drives carcinogenesis, there is a pressing need for effective anti-inflammatory drugs not only to relieve the patients' symptoms but also to prevent CAC. For several years, 5-ASA was supposed to be the most potent chemopreventive drug available. However, available data for the chemopreventive effect of 5-ASA are complex with some studies confirming a protective effect while other studies could not reproduce these findings [26, 34, 35]. Yet, our study demonstrated a decreased risk of CAC development in patients with anti-inflammatory and/or immunosuppressive treatment. Of note, one study reported a higher CAC risk in UC patients with extended duration of 5-ASA medication [36]. Moreover, in our study, patients receiving anti-TNF treatment tended to have a slightly increased risk of carcinoma development. However, one might suggest that patients with continuous need of 5-ASA medication or anti-TNF treatment due to a chronic actively course of disease with ongoing inflammation are at increased risk of CAC due to the comparatively high disease activity. Confirmatively, no increase in CAC in anti-TNF-treated patients has been found yet [37]. In conclusion, 5-ASA treatment in UC patients without active disease, only for reasons of chemoprevention could not be recommended in general [38]. Since inflammation is a crucial factor for CAC development, early aggressive anti-inflammatory therapy is recommended and may include long-term 5-ASA treatment, as well as early anti-TNF treatment or immunosuppressive therapy with azathioprine.

However, even if UC patients are taking a chemopreventive medication, there is still a considerable amount of patients developing CAC. Therefore, endoscopic dysplasia surveillance programs have been developed proposing surveillance in extensive colitis beginning at 8–10 years after onset of disease and in case of left-sided colitis after 15 years, respectively [39–41]. Although accordant surveillance strategies have been implemented in our clinic, data on the stringency of adherence and quality of endoscopic procedures could not be accessed for all patients, since surveillance endoscopies were also carried out in referring medical centers according to patient preferences. Despite the mentioned limitations of this study in correlating extend of disease with development of dysplasia or CAC, our data suggest that a strict classification of pancolitis versus left-sided colitis may not be appropriate in all cases. As a consequence, patients with left-sided colitis and high disease activity may also be screened 8 years after onset of disease. In addition, repetitive endoscopies are not only used for cancer surveillance strategies but have also gained importance with the advent of endoscopic endpoints in the evaluation of treatment efficacy and determination of remission in terms of mucosal healing as a predictor for fewer clinical relapse and lower colectomy rates [42].

Due to the fact that our data are based on a single-center study, the general validity may be limited. However, it is the best way to study regional cohorts and to avoid heterogeneity of large multicenter studies. Furthermore, the observed risk of CAC may be influenced by the individual surveillance strategies, since a tight follow-up program including screening colonoscopy will increase the likelihood to detect CAC. Interestingly, the insightful meta-

analysis by Eaden et al. [8] indicated geographical differences in the risk of CAC with a low or reduced risk of CAC in Scandinavia. In detail, the authors hypothesized that this may be due to true genetic or environmental differences as well as to a more aggressive UC treatment approach in Scandinavia. In addition, the data from Scandinavia were collected from hospitals treating a defined catchment area so that UC patients with different disease severity are included, unlike in tertiary referral centers mostly treating more severe cases of disease [8]. Comorbidity and co-medication might also have an impact on CAC frequency since there are data indicating that aspirin might reduce the risk of CAC [43]. However, the long-term safety still needs to be confirmed. Interestingly, some studies have found an increased risk of CAC in males [15], yet this effect was confined to patients with follow-up greater than 10 years and patients younger than 45 years of age at first diagnosis while other studies found no significant correlation [2, 44]. Although gender-specific differences in malignancy development have been reported in multiple malignancies, including CRC, our study as well could not detect differences, indicating the need for further specific population-based studies to optimize surveillance strategies possibly taking gender-specific risk constellations into account.

In this cohort, an increased risk of CAC was observed. Due to the fact that uncontrolled inflammation is one major source of premalignant alterations, the new IBD treatment paradigm of early intervention (accelerated step up therapeutic strategy) including immunosuppressive therapy might eventually reduce the risk of CAC in the long-term. The role of a lifelong treatment with chemopreventive drugs, as well as appropriate endoscopic surveillance program, still needs to be further elucidated.

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