Dysplasia Associated With Crohn's Colitis

Segmental Colectomy or More Extended Resection?

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Background and Objective: There is limited data on the appropriate management of dysplasia in Crohn's colitis. An evidence-based surgical strategy is provided.

Methods: Patients with a pathologic diagnosis of dysplasia in Crohn's colitis from 1987 to 2009 were identified. Patients were classified by dysplasia grade (low grade or LGD, high grade or HGD). Clinical, endoscopic, operative, and pathologic data were retrieved. Factors associated with a final cancer diagnosis were analyzed. Survival data on patients undergoing limited versus radical resection for cancer and HGD was compared.

Results: From 1987 to 2009, 50 patients underwent a colectomy for Crohn's colitis–associated dysplasia. The predictive value of HGD for a final HGD or cancer diagnosis was 73%. The predictive value of LGD on biopsy for HGD in the colectomy was 36%. Sixteen patients (44%) who underwent a total proctocolectomy (TPC) or subtotal colectomy (STC) had multifocal dysplasia. Four of 10 (40%) cancer patients had evidence of dysplasia remote from cancer site on pathologic examination. During follow-up, there were 3 cancer-related deaths. One patient died of metachronous cancer after STC.

Conclusions: The findings confirm the risk of cancer in patients with CD dysplasia. Because of the multifocal nature of dysplasia in Crohn's colitis, TPC is recommended in good-risk patients. In specific circumstances, such as poor-risk patients especially in the setting of LGD, close endoscopic surveillance or alternatively segmental or STC with close postoperative endoscopic surveillance, depending upon the individual circumstance, may be discussed.

Keywords: Crohn's disease, high-grade dysplasia, low-grade dysplasia, total proctocolectomy, subtotal colectomy, segmental colectomy

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In patients with ulcerative colitis, the presence of dysplasia may lead to progression to colorectal cancer in up to 58% of cases.[1] The risk of cancer progression is highest in patients exhibiting irregular lesions or masses associated with high-grade dysplasia (HGD).[2] More recent studies have demonstrated the risk of cancer in ulcerative colitis patients with flat dysplasia.[3] In patients undergoing colectomy for low-grade dysplasia (LGD), approximately 19% will harbor a concurrent colorectal cancer or HGD.[4] However, there is limited data pertaining to the management and prognosis of dysplasia in Crohn's colitis. In early studies, the reported cumulative prevalence of dysplasia in Crohn's colitis ranged from 2% to 5%.[5,6] Currently, the estimated 25-year risk of dysplasia in Crohn's colitis ranges from 12% to 25%.[7,8] Histopathologic review of colectomy specimens in small case series (<25 cases each) with cancer and Crohn's colitis has identified the presence of carcinoma contiguous with HGD in 56% to 100%.[9–11] Importantly, dysplasia distant from cancer has been identified in 38% to 41% of specimens,[10,11] with distant dysplasia always occurring in an area of colitis.[10] We have recently reported the presence of synchronous dysplasia in 30% of patients with Crohn's colitis–associated carcinoma.[12]

Although there are similarities between Crohn's disease (CD) and ulcerative colitis with regard to the role of endoscopic surveillance[8] and risk factors for the development of colorectal cancer, such as pancolitis and disease duration,[13] the management paradigm for Crohn's-associated dysplasia may not simply be extrapolated from ulcerative colitis-associated dysplasia. In ulcerative colitis patients with dysplasia-associated lesion or mass, HGD, or multifocal dysplasia, total proctocolectomy (TPC) is recommended because of the presence of a "field-change effect" and the consequent risk of colorectal cancer. This radical approach is necessary, but is mitigated by the option of restorative proctocolectomy. In CD, such an approach would frequently result in a permanent ileostomy and it is unknown whether radical surgery represents overtreatment in patients with CD with segmental involvement of the colon. The presence of distant dysplasia, remote from colitis, in such cases would be crucial in the therapeutic decision-making. However, in some situations, it is not possible to satisfactorily advise the patient of these risks, as stricturing CD may prohibit full colonoscopic visualization.[14] Current consensus for the management of symptomatic Crohn's colitis[15–17] recommends segmental resection where possible, but best surgical practice for cancer prophylaxis in CD is less clear.

To date, there have been no published studies on the natural history or management of dysplasia in Crohn's colitis, particularly the subsequent development of colorectal cancer, based on endoscopic and histological risk stratification. The aims of this study were to quantify the risk of colorectal cancer in Crohn's colitis patients with different forms of dysplasia undergoing colectomy and to evaluate whether a segmental colectomy or more extensive resection is required in patients with dysplasia.

METHODS

The study was approved by the institutional review board. All patients with a histological diagnosis of dysplasia and documented evidence of Crohn's colitis, undergoing treatment at Cleveland Clinic Foundation from 1987 to 2009, were included. Patients were identified from a search of our pathology database. Data from original pathology reports were reviewed. Demographic and clinical data were extracted from a prospectively maintained Crohn's Disease Database. Endoscopic and operative reports were retrospectively reviewed.

Study Design

Patients with a preoperative histological diagnosis of dysplasia were evaluated to assess the risk and location of cancer and dysplasia in the colectomy specimen. Patients were described according to the grade of dysplasia (sporadic adenoma, LGD, HGD) in colectomy specimens. For patients with cancer or dysplasia on final pathology, the risk of these findings in other segments in the resected specimen was evaluated. Survival outcomes in patients undergoing resection

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and the risk of synchronous disease were categorized according to the type of colectomy performed (segmental vs extended resection).

Outcome Measurement

The primary outcome was the presence of cancer and dysplasia in pathologically examined colectomy specimens. Risk factors associated with these outcomes were also evaluated.

Inclusion and Exclusion Criteria

Patients were included if they had histological evidence of dysplasia on preoperative biopsy. Only patients with histological, radiological, surgical, or endoscopic features to confirm the presence of Crohn's colitis were included. Patients with CD ileitis without evidence of Crohn's colitis were excluded. Patients who underwent colectomy for cancer were excluded.

Classification of Dysplasia

Histological evaluation of biopsies and colectomy specimens, at the time of treatment, was reported by 2 separate gastrointestinal pathologists. Dysplasia was classified as absent, indefinite, low-grade (LGD), high-grade (HGD), or invasive cancer, based on the criteria of Riddell and colleagues.[18] Invasive cancer was staged using the TNM classification system.[19] Patients with sporadic adenomas occurring remote from colitis and flat dysplasia, where endoscopic and pathological examination confirmed the presence of adenomas (tubular or villous) were analyzed independently from LGD and HGD. The preoperative dysplasia classification was recorded separately from the postoperative diagnosis. Dysplasia site was determined on both preoperative colonoscopy biopsy reports and/or postoperative histopathological examination of colectomy specimens.

Mucosal Findings at Endoscopy

Surveillance and/or diagnostic colonoscopy was performed in patients before colectomy. Surveillance endoscopy was performed using a standardized protocol of random and targeted biopsies. On the basis of endoscopy, appearance of dysplasia was classified as flat or raised. For the purpose of this study, raised appearance of dysplasia is synonymous with dysplasia-associated lesion or mass (DALM).[20] Colitis severity was graded by the endoscopist as absent (in remission), mild, moderate, or severe. Extent of colitis was defined on the basis of anatomical segments and the presence or absence in each segment was recorded (ascending, transverse, descending, sigmoid colon, and rectum).

Study Variables

Patient characteristics included sex; ethnicity; smoking status; age at CD diagnosis and dysplasia; and family history of CD, ulcerative colitis, or colon cancer. Disease factors included CD behavior, presence of ileitis or perianal disease (fistulae, abscess) at the time of surgery, and history of extraintestinal manifestations. Operative details included history of prior surgery, type of resection, and complications. Follow-up data, tumor recurrence, and mortality were recorded.

Statistical Analysis

Categorical variables were summarized as frequencies and percentages. Quantitative variables were summarized as medians with interquartile ranges. Differences between groups were calculated using the χ^2 test for categorical variables and the Wilcoxon test for continuous variables. The effect of type of resection on oncologic outcomes was analyzed using survival data. Statistical analysis was performed using JMP version 8 software (SAS Institute INC, NC). A $P < 0.05$ was considered statistically significant.

RESULTS

From 1987 to 2009, 50 patients underwent colectomy for a preoperative histological diagnosis of dysplasia or biopsies indefinite for dysplasia. Twenty-five patients (50%) had preoperative LGD, 22 (44%) had preoperative HGD, and 3 (6%) had preoperative biopsies that were indefinite for dysplasia. After colectomy, 10 patients (20%) had a final diagnosis of cancer. Median follow-up time from dysplasia diagnosis in patients with cancer was 6 (3.1–7.5) years compared to 2 (0.9–8.5) years in patients with dysplasia alone. Patient characteristics are presented in Table 1 according to the presence of cancer or dysplasia alone in the colectomy specimen. There was no significant association between duration of CD prior to diagnosis of dysplasia or CD phenotype and the presence of cancer in the colectomy specimen.

Endoscopic features and preoperative biopsy findings are shown in Table 2. Thirty-three percent of patients with a raised mucosal appearance at colonoscopy had a final cancer diagnosis ($P = 0.0001$). In contrast, for flat dysplasia, invasive cancer and HGD were found in 13% and 30% patients respectively. Preoperative HGD was significantly associated with a final cancer diagnosis in these patients ($P = 0.0002$). The risk of cancer in the colectomy specimen was 10/22 (45%) for patients with a preoperative diagnosis of HGD alone. None of the patients with a preoperative diagnosis of LGD had cancer in the specimen. The predictive value of HGD on preoperative biopsy for HGD or cancer in the colectomy specimen was 73%. The predictive value of LGD on biopsy for HGD in the colectomy was 36% (0 patients with LGD on biopsy had cancer in the colectomy specimen).

Extended Versus Limited Resection in Patients and the Risk of Metachronous Disease

Twenty-one patients (42%) underwent a TPC, 15 (30%) patients underwent a subtotal colectomy (STC), and 14 (28%) underwent a segmental resection for dysplasia. Sixteen patients (44%) who underwent a TPC or STC had multifocal dysplasia, 8 of these patients (50%) had preoperative LGD, whereas 8 (50%) had preoperative HGD on colonoscopy. Thus, for the patients with preoperative LGD on colonoscopy, the rate of multifocal dysplasia in the colectomy specimen was 32% (8/25). For patients with preoperative HGD, the rate of multifocal dysplasia was 36.4% (8/22). Four of 10 cancer patients (40%) had evidence of dysplasia remote from cancer site on pathologic examination. In 10 cancer patients, the T stage was T1 or T2 in 7 patients and T3 or T4 in 3 patients. One patient had node-positive disease. Cancers in association with dysplasia were found distributed throughout the large bowel; the rectum was involved in 4 patients, the left colon in 3 patients, and the right colon in 3 patients.

Eleven of 26 patients, who underwent colectomy and had cancer or HGD in the specimen, underwent procedures that left them at risk of developing cancer or HGD in the retained colorectum during follow-up. This was a median 6.2 years in patients undergoing segmental colectomy and 4.1 years in patients undergoing STC. Six patients underwent STC and 5 underwent a segmental colectomy. Only 1 of 11 patients developed a metachronous cancer in the rectum 3 years after STC for cancer and died during follow-up. This patient did not comply with rectal surveillance after STC. Patients who were "at risk" of metachronous neoplasia having had limited resections for cancer or HGD had no observed difference in overall survival time by Kaplan-Meier analysis (log rank $P = 0.28$) compared to patients with HGD or cancer undergoing TPC or completion proctectomy. There were no documented occurrences of metachronous HGD in patients who underwent subtotal or segmental colectomy for HGD alone.

During follow-up, there were a total of 2 further cancer-related deaths, both in the TPC group, where 2 patients died of hepatic recurrence.

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TABLE 1. Baseline Characteristics of Patients With a Final Pathologic Diagnosis of Cancer and Dysplasia Versus Dysplasia Alone

	Cancer and Dysplasia	Dysplasia Only	*P*
N	10	40	
Males	5 (50)	30 (75)	0.13
Age at dysplasia	54 (50–59)	53 (39–63)	0.66
Follow-up time (yrs)	6 (3.1–7.5)	2 (0.9–8.5)	0.24
Duration CD prior to biopsy (yrs)	14.8 (7.4–23)	10 (3.3–20)	0.57
Ethnicity			0.16
African	2 (50)	2 (50)	
Caucasian	8 (17)	38 (83)	
Smoking			0.93
Never	5 (19)	22 (81)	
Current	2 (20)	8 (80)	
Past	3 (23)	10 (77)	
FH inflammatory bowel disease			0.53
No	7 (19)	30 (81)	
CD	3 (30)	7 (70)	
Ulcerative colitis	0	3 (100)	
FH colon cancer			0.65
No	8 (21)	30 (79)	
Yes	2 (17)	10 (83)	
Previous diagnosis of ulcerative colitis	4 (21)	15 (79)	0.95
Presence of extra-intestinal manifestations	1 (33)	2 (66)	
CD Phenotype			0.22
Inflammatory	5 (14)	32 (86)	
Stricturing	4 (36)	7 (64)	
Penetrating	1 (50)	1 (50)	
History of ileal CD	40 (73)	15 (27)	0.65
History of perianal CD	2 (29)	5 (71)	0.26

FH indicates family history.

TABLE 2. Preoperative Endoscopic Features and Biopsy Results in Patients With a Final Pathologic Diagnosis of Cancer and Dysplasia Versus Dysplasia Alone

	Cancer and Dysplasia	Dysplasia Only	*P*
Indication for scope			0.34
Surveillance	6 (16)	32 (84)	
Symptoms	4 (33)	8 (67)	
Mucosal appearance			0.0001
Flat	4 (13)	28 (87)	
Raised	6 (33)	12 (67)	
Colitis activity			0.73
Remission	2 (33)	4 (67)	
Mild	2 (15)	11 (85)	
Moderate	4 (24)	13 (76)	
Severe	2 (50)	2 (50)	
Preoperative dysplasia grade			0.0002
LGD	0	25 (100)	
HGD	10 (46)	12 (54)	
Indefinite	0	3 (100)	
Associated polyp			
Tubular adenoma	2 (20)	8 (80)	
Tubulovillous adenoma	0	2 (100)	
Villous adenoma	2 (66)	1 (33)	
Serrated polyp	0	1 (100)	

DISCUSSION

Patients with CD are at increased risk of colorectal cancer,[21] with the risk rising in patients with Crohn's colitis.[22,23] However, there is a paucity of data detailing the genetic mechanisms responsible for tumor progression in CD or the presence of a "field change" effect and as such there is poor evidence to support the practice of TPC in CD once dysplasia is detected.[1,24] The recommendations from guidelines in managing neoplasia in inflammatory bowel disease are therefore not specific to CD and are based on extrapolation of data from ulcerative colitis.[20]

Previous studies which have included patients with Crohn's colitis and dysplasia are listed in Table 3. Only 1 study was conducted

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TABLE 3. Previous Studies Which Included Patients With Crohn's Colitis–Associated Dysplasia

Author	Country	Period of Patient Inclusion	Patients Included	Study Objective	Total Number of Patients in Study	Subset of Patients With Dysplasia or Cancer
Korelitz[14]	USA	1971–81	All patients with CD who underwent rectal biopsy	Pathology review of rectal biopsies in CD for dysplasia	356	18
Choi and Zelig[13]	USA	1957–91	All patients with inflammatory bowel disease associated colorectal cancer	Similarities in patients with Crohn's and ulcerative colitis-associated colon cancer	80	28
Sigel et al[10]	USA	1977–97	All patients with CD associated adenocarcinoma	Pathology review of Crohn's and intestinal cancer	30	22
Maykel et al[26]	USA	1992–2004	All patients operated on for Crohn's colitis	Incidence of dysplasia or cancer in CD colectomy specimens	222	11
Jess et al[25]	USA	1940–2001	Population based inflammatory bowel diseasecohort study	Risk of progression of inflammatory bowel diseasedysplasia to cancer	692	7
Svrcek et al[11]	France	1990–2005	All patients with inflammatory bowel diseaseassociated colorectal neoplasia	Pathology review of inflammatory bowel disease-associated dysplasia and cancer	82	18
Friedman et al[8]	USA	1980–2005	Cohort of patients with chronic Crohn's colitis	Prospective evaluation of surveillance in Crohn's colitis	249	18
Bergeron et al[7]	France	1991–2009	All inflammatory bowel diseasepatients with endoscopic and histologic pancolitis	Risk factors for neoplasia in patients with pancolitis	855	36
Kiran et al[12]	USA	1980–2007	All patients with IBD associated colorectal cancer	Evaluate characteristics of cancer complicating inflammatory bowel disease	240	64

prospectively, in patients with Crohn's colitis undergoing surveillance.[8] The remaining studies have focused on patients with colorectal cancer and inflammatory bowel disease to examine similarities and differences between ulcerative colitis and CD,[12,13] or risk factors for developing neoplasia in colitis.[6,7,25,26] The numbers of patients with actual Crohn's colitis–associated neoplasia in these studies range from 7 to 64, and these studies cannot provide a basis for management decisions for patients with Crohn's colitis–associated dysplasia. This is the first study that specifically brings together clinical, endoscopic, operative, and pathological data from both biopsy and colectomy specimens to establish a decision-making process for patients with Crohn's colitis–associated dysplasia.

We identified a 45% risk of colorectal cancer in the colectomy specimen for patients with a preoperative biopsy confirming HGD. This is similar to data published in ulcerative colitis patients who undergo colectomy for HGD.[27] In patients with LGD, the risk of colorectal cancer was 0% in our study, but there was a 36% risk of HGD in the colectomy specimen. We also identified a strong association between raised dysplasia on preoperative endoscopy and cancer (33% of patients). For flat dysplasia, invasive cancer and HGD were found in 13% and 30% patients, respectively, which are still significant. Both endoscopic appearance and grade of dysplasia can therefore be used to support the decision to proceed to colectomy in patients with dysplasia on biopsy.

To try and identify appropriate situations for the use of limited versus radical surgery for Crohn's colitis-associated dysplasia, we examined the frequency of dysplasia remote from colitis and cancer, as well as multifocal disease. Remote dysplasia in the resected specimen in the presence of cancer was identified in 40% of patients. This group of patients would clearly be vulnerable to metachronous cancer, if a limited resection were performed. The finding that dysplasia was multifocal in 44% patients provides further credence to this concern. A survival benefit could not be determined for patients who underwent TPC in this series, as extended follow-up for patients who underwent "at risk" procedures is necessary for such a difference to be detected. One patient with follow-up, after a surgical procedure that left them at risk of metachronous disease, experienced cancer in the rectal stump 3 years after STC. This patient had a T2 N1 colon cancer at index surgery, contiguous with multifocal HGD.

Risk stratification for initiating endoscopic surveillance in CD using factors such as disease extent, family history, disease duration, and presence of primary sclerosing cholangitis have been identified by previous studies.[7,8,20] These factors were not identified as predisposing to cancer in dysplasia patients in this study.

The availability of high-quality pathological analysis of all biopsies to grade dysplasia and to assess for remote dysplasia and multifocal disease in colectomy specimens, is critical to surgical decision-making. Once pathological and endoscopic features are established, the surgical decision regarding type of operation can be made in the context of CD activity, particularly the likelihood of rectal preservation and ileal disease. The individual patient's wishes to avoid a stoma, life expectancy, and the likelihood of both physician

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and patient compliance with high-quality surveillance,[28] should also be considered.

The information obtained from a relatively large number of patients included in this study helps evaluate some of the previously unanswered questions relating to the risk of cancer, and management of patients with Crohn's colitis with dysplasia. Data presented in this study has been collected over a 22-year period, and in that period, 50 cases were accumulated. The retrospective nature of the study conducted over a prolonged period, however, leads to some limitations. There was discordance between preoperative and postoperative pathology for some patients, whereby 3 patients with HGD on endoscopic biopsy did not have any dysplasia or cancer in the final colectomy specimen. Although the preoperative diagnosis of HGD was made on biopsy in accordance with Riddell criteria for all patients, because these 3 patients underwent surgery before 1995, we were unable to retrospectively review their pathology. Secondly, there were small numbers of patients in some of the subgroups leading to the potential for a type II error. Nevertheless, in the context of unavailability of information from prospective studies and paucity of other reports, this is the most comprehensive study to date, specifically designed to develop evidence-based recommendations for the surgical management of patients with Crohn's colitis with dysplasia. These findings are likely of immense clinical importance, because they help provide evidence that was hitherto unavailable, for the development of the most appropriate surgical strategy for patients with Crohn's colitis with dysplasia and cancer.

This study illustrates the significant risk of cancer in patients with Crohn's colitis with dysplasia, the occurrence of dysplasia in segments not involved by colitis and the importance of considering a proctocolectomy, due to the multifocal nature of cancer and dysplasia in patients with Crohn's colitis. These factors and the association between cancer and raised lesions or dysplasia associated with lesion or mass emphasize the need for surveillance in patients with Crohn's colitis. Current guidelines advocate regular annual or biannual surveillance with extensive mucosal sampling and advanced imaging for targeted biopsies, in patients with disease for more than 8 years. Endoscopic surveillance in patients is likely to lead to earlier detection of neoplastic lesions and may influence survival in patients with Crohn's colitis.[20]

When a diagnosis of Crohn's colitis–associated cancer is known in advance of surgery, a TPC should be strongly considered to eliminate the risk of metachronous disease, because 44% of these patients had dysplasia remote from the site of cancer. For patients with HGD, the 45% risk of cancer supports a similar approach. Whether dysplasia is endoscopically raised or flat further determines this risk, with the risk of cancer being 33% (6 of 18 patients) in patients with raised dysplasia on endoscopy. In select patients with disease confined to the large bowel and no small bowel or perineal disease, the option of an ileoanal pouch may also be considered.[29] In good-risk patients with LGD, a similar approach may be considered because of the risk of multifocality and HGD. In poor-risk surgical patients, those with extensive perineal and small bowel disease, especially in the setting of LGD, alternative options may be entertained, considering the lower cancer risk with LGD. Such options need to be individualized on the basis of an assessment of patient, disease, and endoscopic and pathologic factors. These include close colonoscopic surveillance and biopsies or a segmental or STC with anastomosis and close postoperative endoscopic surveillance especially when surgery is required for concomitant segmental pathology such as colitis or stricture. Although this does not obviate the cancer risk, specific circumstances may define such an approach after due discussion of the risks and benefits. This may also be considered as an alternative option in other patients where a TPC may be too radical or not accepted, especially in the context of the relative cancer risk based on an evaluation of the risk factors discussed earlier. In cases of colitis-associated dysplasia, where intestinal continuity cannot be established after STC, an interval completion proctectomy should be considered as soon as this is feasible. When rectal preservation is possible or decided upon and intestinal continuity is maintained, scheduled annual surveillance with biopsies is recommended.

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