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Prospective Study of the Progression of Low-Grade Dysplasia in Ulcerative Colitis Using Current Cancer Surveillance Guidelines

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Abstract

Background—The goal of this study was to assess the natural history of low-grade dysplasia and its risk of progression in ulcerative colitis (UC) patients by prospective endoscopic surveillance.

Methods—42 UC patients with low-grade dysplasia (LGD) were followed prospectively using a uniform approach to surveillance colonoscopy with an average of 43 biopsies per exam. The interval between colonoscopies ranged from 3–12 months. Progression was defined as development of high-grade dysplasia (HGD) or cancer (CA) at subsequent colonoscopy or at colectomy. Univariate and multivariate analysis were performed to identify risk factors associated with progression.

Results—Patients were followed for an average of 3.9 years (range 1–13). Over that period 19% (8/42) of patients progressed to advanced neoplasia (2 cancers, 6 HGD) while 17% (7/42) had persistent LGD and 64% (27/42) had indefinite dysplasia or no dysplasia at the end of follow-up. Multivariate analysis demonstrated that the number of biopsies with low grade dysplasia at baseline was associated with an increased risk of progression to advanced neoplasia (RR-5.8, 95%CI (1.29–26.04). Among the 15 patients who underwent colectomy, four were found to have higher grade neoplasia on their colectomy specimen that their pre-operative colonoscopy, and these patients were more likely to be nonadherent with recommendations for colectomy.

Conclusions—The majority (81%) of UC patients with LGD did not progress to higher grades of dysplasia during a 4 year follow-up. Patients with 3 or more biopsies demonstrating low grade dysplasia at a single colonoscopy were at increased risk for progression to advanced neoplasia.

Keywords

low-grade dysplasia; ulcerative colitis; neoplasia; dysplasia; colon cancer

Introduction

Patients with ulcerative colitis (UC) have an elevated risk of colon cancer (1). Neoplastic progression is believed to occur in a step-wise fashion from inflammation without dysplasia → indefinite for dysplasia → low-grade dysplasia → high-grade dysplasia → cancer. Our

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current approach to cancer prevention in UC involves periodic colonoscopy with random biopsies, with the goal of detecting precancerous changes at an early enough stage to prevent the complications of invasive cancer. While experts are generally in agreement that high-grade dysplasia and cancer are indications for colectomy, the optimal management of UC patients with low-grade dysplasia (LGD) remains controversial. Some experts cite a 20% risk of a missed HGD or cancer at colectomy, and up to a 50% risk of progression to advanced neoplasia over 5 years as an indication for colectomy in the setting of LGD (2–5). By contrast, other experts point to reports of a lower rate of neoplastic progression, and studies showing that most dysplasia is endoscopically visible, as evidence that heightened surveillance is a safe and appropriate management strategy. (6–10). In general, these previously published studies can be limited in interpretation because of the study design: they were not performed prospectively using the UC colon cancer surveillance guidelines (11).

The colon is a large organ with a surface area in the range of 0.5 to 1.0 square meters. Dysplasia may arise anywhere within this large area, and frequently produces no endoscopically visible lesion. Therefore, an important consideration in investigating the natural history of neoplastic progression in ulcerative colitis is how well the colon was sampled. The number of biopsies taken, and the likelihood that dysplasia will be detected if present within the colon, are directly related. A recent modeling study of dysplasia in ulcerative colitis calculated that the sensitivity of detecting dysplasia involving at least 5% of the colon increased from 60% to 90% when the number of biopsies increased from 18 to 45. (12). To date, nearly all of the studies regarding the outcomes of LGD in ulcerative colitis patients have been performed retrospectively, in patients who had a mixed variety of surveillance protocols, often with relatively few biopsies obtained at colonoscopy. A recent meta-analysis of 20 high-quality surveillance studies reported that the average number of biopsies per colonoscopy was 18, with a range of 9–24 (13). In this analysis, the number of biopsies per colonoscopy was the only variable that had a significant effect on the detection of advanced neoplastic lesions. Thus, under-sampling of the colon during surveillance could well explain the finding in some studies of unsuspected and undetected colon cancer at colectomy. The natural history of dysplasia prospectively followed by an extensive biopsy protocol (consistent with current guidelines) has not been previously reported and may not be the same as dysplasia detected with fewer biopsies(12). It is imperative that we understand more fully the risk of progression in UC-associated dysplasia, as the prevalence of LGD will likely increase with the introduction and widespread adoption of chromoendoscopy and other enhanced endoscopic detection techniques.

While colectomy may be the most widely used method for managing patients with low-grade dysplasia, many patients are reluctant to undergo this surgery. Patients who have had UC for twenty years, which is the average duration of disease prior to the development of dysplasia, often have minimal or no symptoms, and convincing them that a colectomy will improve their quality of life may be difficult (14). Moreover, colectomy is not a benign procedure and side-effects including incontinence, adhesions, infertility/impotence and decreased fecundity can occur.

An informed discussion of the risks and benefits of colectomy versus surveillance for low-grade dysplasia requires an understanding of its natural history. Important questions remain about the biology of low-grade dysplasia: *Does low-grade dysplasia always progress to cancer? If so, over what time interval? Does low-grade dysplasia ever regress? Is high-grade dysplasia always an intermediate step between low-grade dysplasia and cancer? If so can it be detected with confidence? Do any patient characteristics predict progression to high-grade dysplasia or cancer?* We can provide some of the answers to these questions with our prospective study of the natural history of low-grade dysplasia in 42 UC patients who have

been followed by surveillance colonoscopy using a standardized protocol of 4 quadrant biopsies every 10 cm and additional targeted biopsies of mucosal irregularities.

Materials and Methods

Patients

All patients provided written informed consent prior to enrollment in this study. Forty-two patients who had low-grade dysplasia (LGD) followed at the University of Washington between 1987 and 2002 were enrolled and followed prospectively. Entry into the study required that a patient have an established diagnosis of ulcerative colitis with pancolonic distribution for 8 years or more. Patients with coexisting primary sclerosing cholangitis (PSC) were enrolled at the time of diagnosis of UC, regardless of the duration of disease. Most patients were referred in with newly diagnosed LGD from outside institutes for continued management of the dysplasia rather than developing dysplasia while under surveillance. If a patient with LGD was referred for entry into the study, the outside pathology slides were reviewed by one of 2 study pathologists (the late Dr. Rodger Haggitt or Dr. Mary Bronner) to confirm the diagnosis. At the time of enrollment all patients, including those referred from outside providers, underwent a protocol colonoscopy at our institution with an average of 43 biopsies (see below) and had at least 1 biopsy demonstrating LGD. Only the patients who underwent at least two protocol surveillance colonoscopies were included in this study.

At the time of enrollment, the average age of the patients was 49 years (range 26–71) and the average duration of UC was 18 years (range 1–39) (table 1). Eleven LGD patients had PSC as determined by typical cholangiographic abnormalities. The reason for the high percentage of PSC/UC in our cohort is probably twofold: 1) UC patients with primary sclerosing cholangitis are 5 times more likely to get dysplasia than UC patients without it, so they are more likely to be represented in a study of LGD patients; 2) we have a large hepatology and liver transplant referral services.

Dysplasia was categorized as flat (or invisible) if detected only on random biopsies without an endoscopically recognizable lesion. Raised dysplasia was defined as an endoscopically visible lesion for which targeted biopsies were obtained. A colectomy was recommended for all patients who developed high-grade dysplasia (HGD) and for patients who had LGD within a visible lesion that was not amenable to complete endoscopic resection. LGD patients with extensive polyposis or irregularities in the colon were advised to undergo colectomy because of the difficulty of performing surveillance under such conditions. Colonoscopy at 3–6 month intervals was recommended for patients with HGD who declined colectomy; otherwise surveillance colonoscopy for LGD patients was performed every twelve months. Progression was defined as the development of HGD or cancer in a subsequent surveillance colonoscopy or at colectomy.

Protocol Colonoscopy and Colectomy Specimens

The entire colon was evaluated with random biopsies obtained in 4 quadrant fashion every 10 cm during withdrawal from the cecum to the rectum, yielding an average of 40 biopsies per colonoscopy. Some operators use a protocol that included increased random biopsies taken in the recto-sigmoid regions (every 5cm). Additional targeted biopsies were taken from raised or depressed mucosal irregularities or polyps. If amenable to resection, polyps were removed in entirety with snare or cold biopsy forceps. Mucosal biopsies were unrolled from the forceps and oriented submucosal side down on monofilament plastic mesh prior to fixation. The four biopsies taken at each level were placed into Hollande's fixative and the location of the biopsies noted. Biopsy number was determined based on the endoscopists

count of the biopsies at the time of the exam and verified by the number of biopsies counted in pathology jars.

Colectomy specimens were sampled in a grid-like fashion from cecum to rectum. “Lift and snip” biopsies were obtained in a grid-like pattern every 2–3 cm for an average of 120 biopsies per colectomy specimen. Additional samples were obtained from any grossly visible mucosal abnormality.

Histology

All biopsy specimens were evaluated independently by two experienced gastrointestinal pathologists (Dr. Mary Bronner and the late Dr. Roger Haggitt) who had no knowledge of the clinical history or colonoscopic findings. The diagnosis of UC and diagnosis and grading of dysplasia was made by histologic criteria as previously described (15). Dysplasia was identified according to the Dysplasia Morphology Study Group (DMSG) criteria, except that the category of indefinite was not subdivided. Drs. Haggitt and Bronner performed comparative assessment of histologic grading of dysplasia and had 90% concordance. The rare disagreements in histologic assessment were resolved by consensus.

Statistical methods

Statistical analyses were performed using Stata 11 (College Station, TX). Odds ratios and p-values associated with progression were calculated using the chi-squared test, Student’s t-test and Cox proportional hazard modeling. Progression was defined as the development of advanced neoplasia (HGD or cancer) at any time during surveillance colonoscopy or colectomy. The index date was defined as the date of the first protocol colonoscopy in our surveillance program, and the follow up time was calculated as the time from the index date to progression or the date of last colonoscopy, whichever occurred earlier. Each potential risk factor was tested individually for its association with progression to HGD/cancer (univariate analyses). Multivariate analysis of all variables or large subsets of variables is not reported, since the small sample size would result in lack of precision for these results. Continuous variables such as age and numbers of biopsies with low-grade dysplasia were analyzed as continuous variables, and also as dichotomized variables using predetermined cutoff points. Progression curves for the patient groups were estimated using the method of Kaplan and Meier (16).

Ethical Considerations

This study was conducted with the approval of the institutional review board of the University of Washington.

Results

Patients who progressed to advanced neoplasia (Tables 2 and 3;)

The 42 LGD patients were maintained in surveillance for 1–13 years (mean 3.9 years), and none were lost to follow-up. Eight of the 42 LGD patients progressed (2 Cancer and 6 HGD) (Progressors). Thirty-four patients (81%) maintained LGD or downgraded to indefinite or negative for dysplasia (Non-Progressors). The LGD Progressors had a mean age of 44 years, with a mean duration of 16 years of colitis at the time of entry into the study (Table 3). The total follow-up surveillance time between the Progressors and Non-Progressors was similar (3.2 versus 4.0 years, respectively, p=0.55). The patients who progressed from LGD to HGD did so after a mean of 1.8 years (range 1–4 years) after the exclusion of an outlier patient who developed HGD 13 years after initial discovery of LGD (Table 2).

Risk Factors for Progression

The characteristics of the LGD progressors versus non-progressors are outlined in Table 3. Four of the 8 progressors had three or more biopsies demonstrating LGD at entry into the study, compared to 5 of the 32 non-progressors. Patients with 3 or more separate biopsies showing LGD were 5.8 times more likely to progress at any point in time than patients with fewer than 3 biopsies with LGD (p=0.02, 95% CI= 1.3–26.0). Patients with 2 or more biopsies demonstrating LGD showed a trend toward higher likelihood of progression, but this did not meet statistical significance (RR 7.2, 95% CI 0.86–60.07, p=0.07). Younger patients and those with a shorter duration of disease tended to have higher rates of progression; these continuous variables approached statistical significance (age at LGD diagnosis: 44 vs 51 yrs ((RR 0.95, 95%CI 0.88–1.02, p=0.13) and duration of disease: 15.5 vs 18.5 yrs, (RR 0.95, 95%CI 0.88–1.20, p=0.17). Such effects could be mediated through the single age-at-onset variable, however this was not a statistically significant risk factor (p=0.79).

Four of the 8 patients who progressed had PSC; the presence of this condition showed a tendency for increased risk of progression from LGD to HGD/Cancer that was not statistically significant (RR 1.78; 95%CI 0.39–8.11, p=0.45). Ursodiol use was less common among PSC patients who progressed (1 out of 4 patients) compared to 5 of 7 PSC patients who did not progress, suggesting a protective effect from ursodiol.

Progressors and non-progressors were equally likely to have dysplasia in an endoscopically visible lesion versus flat (50% vs 56%, RR 0.61, 95%CI 0.14–2.73, p=0.51), followed by colonoscopy for similar durations (3.2 versus 4 years) and had similar numbers of biopsies taken at each exam (39 versus 43 average per colonoscopy).

Patients who did not progress (Table 3;)

Thirty-four of the LGD patients (81%) did not develop HGD/cancer on subsequent colonoscopies. Seven patients continued to have LGD (17% of the LGD cohort), while 9 patients (21%) had biopsies that became indefinite for dysplasia and 18 patients (43%) were negative for dysplasia at their last colonoscopy. These patients were followed over an average follow-up of four years (range 1–5 years). The patients who did not progress had a mean age of 51 years and a mean duration of 18.5 years of colitis at the time of entry into the study. Seven of the 34 patients had PSC. We evaluated the PSC patients as a subgroup of the LGD cohort and found that UC/PSC patients who had ever had ursodiol treatment were at less risk of progression, with a risk ratio of 0.35 (p=NS).

Twenty-nine of the 34 patients who did not progress had only 1 or 2 biopsies with LGD at the initial colonoscopy. One particular exception was patient UC-8, who had LGD and aneuploid DNA content in nearly every biopsy at entry into the study. Biopsies taken at the subsequent colonoscopy one year later were interpreted as showing only widespread changes of indefinite for dysplasia and had a diploid DNA content. The third year of surveillance, the biopsies were negative for dysplasia with a single focus of indefinite for dysplasia. There was no change in the degree of histologic inflammation in the biopsies from any of the colonoscopies from this individual. This patient had not been taking ursodiol.

Patients Who Underwent Colectomy

Fifteen patients underwent colectomy during the follow-up period (Table 4). A colectomy was recommended for LGD patients who 1) developed HGD, 2) developed an unresectable dysplastic mass at colonoscopy, 3) developed ≥3 biopsies with LGD at a single colonoscopy, and 4) in patients who had sufficient (inflammatory) polyposis to make

surveillance risky. In addition, 7 LGD patients underwent colectomy because of symptoms or tiring of surveillance. The histologic diagnosis in the colectomy specimens showed a similar or lower grade of dysplasia than the last colonoscopy in 11 of 15 patients. Four patients had higher grades of neoplasia at colectomy than found at the last colonoscopy: 1 patient with HGD delayed colectomy for 6 months and had cancer at colectomy (Dukes A) and 2 patients with LGD had HGD at colectomy—one of these patients delayed surgery for 2 years. One of the 15 patients had an endoscopically non-resectable 8cm dysplastic (LGD) mass at colonoscopy that was presumed, and then confirmed to be, Dukes A cancer. This patient had been non-compliant with recommended colonoscopic exam intervals.

Discussion

This study provides valuable data on the natural history of low-grade dysplasia in ulcerative colitis patients who undergo surveillance, and to our knowledge this is the only prospective study with an extensive biopsy protocol that adheres to current recommendations in terms of the number of biopsies obtained and intervals of exams. A modeling study of dysplasia in ulcerative colitis determined that 18 biopsies (the average number reported in a recent meta-analysis) has only 60% sensitivity to detect dysplasia involving 5% of the colon (12, 13). The sensitivity increased to 90% with a protocol involving 45 biopsies. The average number of biopsies per colonoscopy in this study was 43 which provides reasonable confidence that dysplasia was not missed due to under-sampling. Biopsy number in our study was based on the number of biopsies counted by the endoscopist and verified by a count of the specimens in pathology jars.

During follow-up averaging 3.9 years, 19% of the LGD patients progressed, usually over a short time period (mean of 18 months; range 1–3 years). This rapid progression suggests that surveillance intervals exceeding one year in LGD patients could result in failure to detect a HGD intermediate step and result in the patient developing cancer. An important finding in this study is that multifocal dysplasia (≥3 biopsies with LGD) is associated with a nearly 6-fold increased risk of progression to advanced neoplasia. This finding can be helpful for both patients and providers in guiding the discussion about risks and benefits of ongoing surveillance versus colectomy in the setting of LGD. The average age of the patients who progressed was 7 years *younger* than that of those who did not progress (44 versus 51 years, respectively), and progressors had a slightly shorter duration of disease at the time of LGD diagnosis (15.5 versus 18.5 years), but these differences did not reach statistical significance. These findings are consistent with prior studies showing a younger age of onset is associated with an increased risk of dysplasia, and that prevalent dysplasia may carry a higher risk of progression than incident dysplasia. Also consistent with prior studies, we found that ursodiol use in our cohort had a chemoprotective effect against progression to advanced neoplasia among the subset of patients with PSC (17, 18). These findings suggest our patient cohort is similar to previously described LGD patient cohorts and adds to the external validity of the study.

Four out of five patients with LGD at baseline did not progress. Among the 34 patients who did not progress, 18 (53%) had biopsies that were negative for dysplasia at the end of the follow-up period and 9 (26%) were indefinite for dysplasia, suggesting dysplasia can often regress. While it is tempting to attribute the loss of low-grade dysplasia in subsequent colonoscopies to sampling error, a sufficient number of biopsies were obtained at each colonoscopy to make this statistically unlikely (4).

Diagnosis and surveillance of LGD in patients with UC is difficult at best and is complicated by uncertainty with regard to endoscopic detection, histologic interpretation, and natural history of progression. Although colectomy is an effective cancer prevention strategy, the

majority of patients are reluctant to undergo this surgery. Removal of the colon is not a completely benign event: J-pouch failure, adhesions, and incontinence are all complications of the surgery (19). Women who have undergone restorative proctocolectomy have a markedly decreased capability to get pregnant (50–80% decrease in fecundity) (20, 21). What should be the management of a woman with a single focus of LGD who wants to have children? Clearly, more knowledge of the natural history of low-grade dysplasia is essential to make informed decisions.

An informed discussion of the risks and benefits of colectomy for low-grade dysplasia requires an understanding of its natural history. The prospective data presented here provide important information that can guide the discussion with patients who have low-grade dysplasia and are undergoing surveillance colonoscopy with extensive biopsy procurement. *Do all patients with low-grade dysplasia develop cancer?* About one-fifth of patients progress to high-grade dysplasia in the short-term. *If so, over what time interval?* Usually during the ensuing 18 months (1–3 years). *Does low-grade dysplasia ever regress?* In some patients it does appear to regress, however longer term studies are pending to determine whether this change is permanent. *Is high-grade dysplasia usually an intermediate step between low-grade dysplasia and cancer?* Probably, however, when few biopsies are taken at surveillance it could be easily missed. Even with extensive biopsy sampling, one cannot absolutely rule out the development of a cancer; however it would appear that the risk may be reduced with extensive sampling. *Do any patient characteristics predict progression to cancer?* Patients who have 3 or more biopsies with low-grade dysplasia are more likely to progress to high-grade dysplasia. Lastly, there appears to be a reduced risk of progression in LGD patients who are taking ursodiol.

The strength of this study is not only its prospective nature, but also the uniform colonoscopy protocol that provides sufficient biopsies to have confidence that cancer and high-grade dysplasia are not being missed. Limitations of this study design include the modest sample size and limited duration of follow-up, and further prospective data are needed to confirm our findings. Additionally, this study does not distinguish between incident and prevalent dysplasia, a feature that is increasingly recognized as having prognostic implications. Lastly, while the study was not performed using enhance imaging such as chromoendoscopy or NBI, the optics of both the LCD screen and the white light video endoscope have improved over the past decade and may have led to improved dysplasia detection in the latter years of the study. The findings of this study are limited to the natural history of low-grade dysplasia and do not apply to patients with high-grade dysplasia.

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Table 1

Patient Characteristics at Baseline

Age (years)	49.7
Age at UC diagnosis	31.5
Duration of disease	17.9
# biopsies taken (mean)	42
Yrs of follow up	3.9
Primary Sclerosing Cholangitis	11
Ursodiol therapy in PSC/UC	6/11
Left sided dysplasia	20
Multifocal dysplasia	19
Progression to HGD/Cancer	8

*T*one UC control with PSC –Urso data not available

Table 2

Details of LGD Patients who Progressed to HGD or CA

Patient	# of LGD sites*	Duration of UC (yrs)*	Dx at last scope	Dx at colectomy	Time to Prog^	Age at UC onset	Age at LGD*	PSC	Urso
Prog-1	1	29	Mass LGD	CA	13.5	16	45	Yes	no
Prog-2	3	10	HGD	HGD	1	38	48	No	
Prog-3	1	10	LGD	HGD	1.5	16	26	No	
Prog-4	5	16	HGD	HGD	1	17	33	Yes	no
Prog-5	2	21	HGD	LGD	1	21	42	No	
Prog-6	2	26	LGD	HGD	4	31	57	Yes	no
Prog-7	3	10	HGD	NEG	1	56	64	No	
Prog-8	4	4	HGD	CA	3	29	33	Yes	yes

*At the time of initial colonoscopy at study entry.

^Mean follow-up time was 3.2 years, median 1.4 years

Table 3

Characteristics of LGD patients: Progressors versus Non-Progressors

Risk factor	Progressors (n=8)	Non-progressors (n=34)	Risk Ratio [95% CI]†	p value
Average age UC onset (yrs)	28	32	0.99 (0.93–1.05)	0.79
Onset of UC age ≥ 30	3	15	1.12 (0.25–5.09)	0.88
Average age at LGD (yrs)	44	51	0.95 (0.88–1.02)	0.13
Age at LGD ≥ 50	2	17	0.99 (0.10–2.57)	0.40
Duration of UC (yrs) at LGD	15.5	18.5	0.95 (0.88–1.02)	0.17
Duration of UC ≥ 20yrs	3	17	0.36 (0.07–1.87)	0.23
# biopsies taken (mean)	39	43	0.97 (0.92–1.03)	0.34
# of biopsies with LGD(mean)	2.6	1.5*	2.83 (1.44–5.55)*	<0.01
≥2 biopsies with LGD	6	13	7.2 (0.86–60.07)	0.07
≥3 biopsies with LGD	4	5	5.8 (1.29–26.04)	0.02
Left-sided dysplasia	4	16	1.14 (0.25–5.13)	0.86
Visible lesion	4	19	0.61 (0.14–2.73)	0.51
Primary Sclerosing Cholangitis	4	7	1.78 (0.39–8.11)	0.45

† 95% Confidence Interval

* one outlier patient with 40 biopsies of LGD was excluded from calculations

Table 4

Concordance of colonoscopy with colectomy

Grade @ last scope	Colectomy diagnosis	Comments
HGD	CA	Colectomy recommended 6 months prior
LGD in 8 cm mass	CA	Refused regular surveillance intervals
HGD	HGD	
HGD	HGD	
HGD	LGD	
HGD Polyp	NEG	Polyp completely resected at colonoscopy
LGD	HGD	
LGD	HGD	Colectomy recommended 2 yrs prior
LGD	LGD	
LGD	LGD	
LGD	IND	
IND	NEG	
IND	NEG	
NEG	IND	
NEG	NEG	

Colectomy was performed for HGD (5 patients), LGD in unresectable mass (2 patients), multifocal LGD in ≥ 3 biopsies (1 patient), or persistent symptoms or tiring of surveillance (7 patients).