Misclassification of Dysplasia in Patients with Inflammatory Bowel Disease: Consequences for Progression Rates to Advanced Neoplasia

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Background: The natural behavior of flat low-grade (LGD) and indefinite dysplasia (IND) in patients with inflammatory bowel disease (IBD) remains uncertain and seems to be dependent on the interpretation of the pathologist. We studied the progression rate of flat LGD and IND to advanced neoplasia (high-grade dysplasia [HGD] or colorectal cancer [CRC]) before and after histopathological review by a panel of gastrointestinal expert pathologists.

Methods: A nationwide pathology database was used to identify IBD patients with dysplasia in six Dutch university medical centers between 1990 and 2006. Medical charts of patients with recorded flat LGD or IND were reviewed. Histological slides from three university medical centers were reviewed by a panel of three expert gastrointestinal pathologists.

Results: We identified 113 flat LGD patients and 26 flat IND patients. Advanced neoplasia was found in 18 flat LGD patients (16%) after a median follow-up of 48 months, resulting in a 5-year progression rate of 12%. Five IND patients (19%) developed advanced neoplasia after a median follow-up of 24 months, resulting in a 5-year progression rate of 21%. Review of 1547 histological slides from 87 patients resulted in an increase of the 5-year progression rate of flat LGD to advanced neoplasia to 37%, whereas the progression rate of IND decreased to 5%.

Conclusions: A diagnosis of flat LGD that is confirmed by a panel of expert gastrointestinal pathologists is associated with a substantial risk of progression to advanced neoplasia, while confirmed IND is associated with a low risk of progression.

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Key Words: Key Words: inflammatory bowel disease, dysplasia, colorectal cancer

Patients with longstanding ulcerative colitis (UC) or Crohn's disease of the colon (CD) are at increased risk of developing colorectal cancer (CRC).[1–3] Colitis-associated CRC is supposedly developing along an inflammation-dysplasia-carcinoma sequence.[4] Dysplasia is classified microscopically as low-grade (LGD), high-grade (HGD), or indefinite dysplasia (IND).[5] HGD is associated with a high risk of synchronous or metachronous CRC[6] and is therefore generally considered an unambiguous indication for colectomy. Decision-making in case of flat LGD and IND, however, is not straightforward. Progression rates of flat LGD to HGD or CRC varied greatly in previous reports, ranging from no progression to 5-year progression rates of more than 50%.[7–10] These diverging results may have their origin in the selections of study populations and design and endoscopy-related matters. Another pivotal contribution to this phenomenon, however, may be the (mis)interpretation of the pathologists when grading dysplasia. Dysplasia in the indefinite and low-grade categories in particular is associated with a poor interobserver agreement.[11,12] The impact of the different interpretations of dysplasia on the progression rate of flat LGD is unknown. Moreover, data on the natural course of IND are scarce. We studied the frequency of progression of flat LGD and IND to advanced neoplasia (HGD, CRC) before and after histopathological review of

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the diagnosis by a panel of expert gastrointestinal (GI) pathologists. Furthermore, we determined which clinical factors were associated with the risk of progression.

MATERIAL AND METHODS

Study Population

The nationwide pathology archive (PALGA), containing all pathology reports from the Netherlands dating back to 1971, was used to identify patients with inflammatory bowel disease (IBD)-related dysplasia. The PALGA database has a complete nationwide coverage since 1990. A PALGA search for diagnoses of IBD and dysplasia or atypia was performed in six Dutch university medical centers for the time period of January 1990 until April 2006, using diagnostic terms in line with SNOMED terminology. The following combinations of search terms were used to search for dysplasia: colon AND all epithelial dysplasias, colon AND atypia, rectum AND all epithelial dysplasias, and rectum AND atypia. These terms were combined with the following terms to search for dysplasia in patients with IBD: colitis, ulcerative colitis (UC), indeterminate colitis, idiopathic colitis, and Crohn's disease (CD). Only patients with LGD or IND in flat mucosa were included in this study. A biopsy was defined as "flat" when the histopathological diagnosis of LGD or IND was made in a biopsy that was taken from endoscopically normal mucosa, as documented in the colonoscopy report. Patients were recruited in the study at the first time flat LGD or IND was detected. Patients with LGD or IND in raised or otherwise suspect mucosa, those who were diagnosed with HGD or CRC previously or synchronously at the time of flat LGD/IND diagnosis, patients with a previous or concomitant subtotal or total colectomy, patients without any endoscopic or surgical follow-up, and patients with incomplete or missing medical charts were excluded.

Data Collection

A single reviewer collected the following characteristics from medical charts, endoscopy, pathology, and surgery reports: gender, date of birth, date of IBD diagnosis, presence of primary sclerosing cholangitis (PSC), date of diagnosis of flat LGD or IND, location of flat LGD or IND, maximum endoscopic and histological extent of disease, the finding of LGD or advanced neoplasia during follow-up, and duration of follow-up. Disease extent was defined as the maximum extent according to histology and endoscopy reports. In UC patients or patients with indeterminate colitis (IC), proctitis was defined as disease limited to the rectum, left-sided colitis as disease proximal to the rectum but distal to the splenic flexure, and extensive colitis as disease proximal to the splenic flexure. In CD patients, disease extent was defined as ileal if disease was located in the ileum, colonic if disease was located in the colon, and ileocolonic if disease was located in both the ileum and colon. Dysplasia was considered "unifocal" if only one specimen jar contained dysplasia and "multifocal" if two or more specimen jars contained dysplasia. Advanced neoplasia was defined as the finding of HGD or CRC in a biopsy or colectomy specimen. Progression was defined as the development of advanced neoplasia during follow-up. Duration of follow-up was measured in months and defined as the time from first flat LGD/IND diagnosis to one of the following endpoints: 1) end of follow-up (1st of December 2007); 2) death; 3) subtotal or total colectomy; or 4) lost-to-follow-up. When dysplasia was found during follow-up, location, grade, and mucosal appearance were documented. When CRC had evolved, location, stage, and therapy were documented.

Pathology Review

Histology slides from patients with flat LGD or IND were retrieved from three academic centers. The selection of centers for histopathological review was based on the availability of histological slides from these centers. All slides belonging to the original pathology reports that reported dysplasia or CRC were distributed among three expert GI pathologists (J.A.O., F.J.Wt.K., M.E.I.S.) and reviewed by one of these three pathologists in a blinded fashion. Slides were reviewed according to the criteria and definitions as articulated by Riddell et al.[5] Each slide was scored as negative, positive, or indefinite for dysplasia, and in case of positive for dysplasia as LGD or HGD. The indefinite category was subdivided into "probably positive" and "probably negative." The most advanced degree of neoplasia observed in a histological slide during review and the relation to the underlying IBD was documented. When a pathologist doubted the degree of dysplasia or when disagreement existed between the original and the revised diagnosis, slides were discussed and reassessed by all three pathologists during a regularly scheduled meeting in order to obtain a consensus diagnosis. We compared original diagnoses with revised diagnoses and assessed progression rates before and after histopathological review. Patients with missing slides containing dysplasia according to the original diagnosis were excluded from further follow-up analysis.

Statistical Analysis

Patients were entered in this study at the first finding of flat LGD/IND and were followed for the progression to advanced neoplasia. Time to progression was measured in months. Patients who did not develop HGD or CRC during follow-up were censored at the moment of the last colonoscopy or colectomy. Five-year progression rates were calculated using Kaplan–Meier survival analysis and

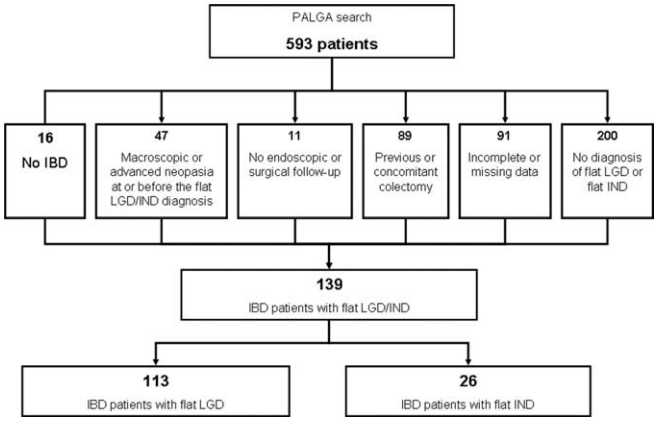

FIGURE 1. Flowchart of PALGA search.

comparisons between progression rates were made using log-rank testing. Univariate and multivariate testing was performed using Cox regression analysis. Proportions were compared using the chi-square test or Fisher's exact test, where appropriate. Continuous variables were compared using Student's *t*-test or Mann–Whitney *U*-test, where appropriate. A P-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS 15.0 for Windows (Chicago, IL).

Ethical Considerations

This study was carried out with the approval of and in accordance with the ethical guidelines of the research review committee of our institution.[13]

RESULTS

Patients

Our search yielded 593 IBD patients with dysplasia or atypia in the initial report. Review of medical charts, endoscopy, pathology, and surgery reports resulted in exclusion of 454 patients, leaving 113 IBD patients with flat LGD and 26 IBD patients with IND for further analysis. The reasons of exclusion are shown in the flowchart (Fig. 1).

Progression of Flat LGD to Advanced Neoplasia Before Review

An initial diagnosis of flat LGD was made in 92 UC patients (81%), in 18 CD patients (16%), and in three IC patients (3%). Clinical characteristics of these patients are shown in Table 1. In more than half of the patients, flat LGD was found to be unifocal, predominantly located in the rectum. Forty patients had multifocal flat LGD, which was located distally to the splenic flexure in 22 patients (55%). Patients were followed for a median duration of 71 months (range, 0–209). In the whole group of 113 patients with flat LGD, 18 patients (16%) developed advanced neoplasia. Eleven patients progressed to HGD, five of whom developed CRC subsequently. Of these five patients, three were operated on after the detection of HGD and CRC was found in the surgical specimen. In one patient, CRC was found during colonoscopy performed 4 months after the detection of HGD, while in another patient CRC was diagnosed after 11 years during a follow-up endoscopy. In another two patients HGD and CRC were detected synchronously. Five patients progressed to CRC without prior HGD. In 16 patients (89%), colectomy was performed, whereas in one patient only the rectum harboring CRC was resected. Another patient underwent a transanal endoscopic microsurgery procedure to resect a nonadenoma-like DALM with HGD. In six patients with no endoscopic or histological evidence of progression, advanced neoplasia was found in the colectomy specimen. Median time to progression was 48 months (range, 1–169 months). The 5-year progression rate to HGD or CRC for all 113 patients with flat LGD was 12% (95% confidence interval [CI], 0.05–0.19) (Fig. 2).

In 95 patients no progression to HGD or CRC was found during a median duration of follow-up of 65 months (range, 0–209) and a median of three colonoscopies per patient (range, 0–24). In 27 patients (28%) one or more foci of LGD were detected during follow-up, but none progressed to HGD or CRC.

Progression of IND to Advanced Neoplasia Before Review

IND was initially found in 21 UC patients (81%), four CD patients (15%), and one IC patient (4%). Clinical characteristics of these patients are shown in Table 1. Unifocal flat IND was identified in 17 patients (65%), all located in the left colon. Multifocal IND was found in seven patients (27%) and was distributed over all segments of the colon. Patients were followed for a median duration of 54 months (range, 0–111). Five UC patients (19%) progressed to advanced neoplasia over a median time of 24 months (range, 2–101). All five patients developed HGD. In one of these patients concurrent CRC was found, whereas in another patient CRC was diagnosed later on. All five patients underwent colectomy. In one patient HGD was detected in the colectomy specimen, following resection for therapy refractory disease. In both CRC cases the colectomy was performed because of HGD with CRC identified in the colectomy specimen. The 5-year progression rate to HGD for all 26 patients with flat IND was 21% (95% CI, 0.02–0.40) (Fig. 2).

Twenty-one patients (81%) showed no progression to advanced neoplasia during a median follow-up of 62 months (range, 0–111) and a median of two colonoscopies (range, 0–6) per patient. In eight patients (38%) one or more foci of LGD were found during follow-up, but none progressed to HGD or CRC.

TABLE 1. Patient Characteristics of Flat LGD and IND Patients Before Histopathological Review of Dysplasia

Variable	Flat LGD $N = 113$	IND $N = 26$
Sex		
Male	60 (53%)	19 (73%)
Female	53 (47%)	7 (27%)
IBD diagnosis		
Ulcerative colitis	92 (81%)	21 (81%)
Crohn's disease	18 (16%)	4 (15%)
Indeterminate colitis	3 (3%)	1 (4%)
Median age at diagnosis (yr, range)	28 [7-78]	25 [13-66]
Median age at initial dysplasia diagnosis (yr, range)	41 [12-78]	37 [18-73]
Median duration of IBD at initial dysplasia diagnosis (yr, range)	11 [0-43]	14 [0-30]
Extent of IBD		
Ulcerative colitis – Proctitis	1 (1%)	1 (5%)
Ulcerative colitis – Left-sided	16 (17%)	6 (29%)
Ulcerative colitis – Extensive	75 (82%)	14 (76%)
Crohn's disease – Colonic	11 (61%)	3 (75%)
<50% of colon	1 (9%)	0 (0%)
>50 % of colon	10 (91%)	3 (100%)
Crohn's disease – Ileocolonic	7 (39%)	1 (25%)
<50% of colon	1 (14%)	0 (0%)
>50% of colon	6 (86%)	1 (100%)
Indeterminate colitis – Proctitis	0 (0%)	0 (0%)
Indeterminate colitis – Left-sided	0 (0%)	0 (0%)
Indeterminate colitis – Extensive	3 (100%)	1 (100%)
Location of dysplasia		
Unifocal	61 (54%)	17 (65%)
Rectum	30 (49%)	8 (47%)
Sigmoid	15 (25%)	7 (41%)
Descending colon	8 (13%)	2 (12%)
Transverse colon	2 (3%)	0 (0%)
Ascending colon	3 (5%)	0 (0%)
Cecum	3 (5%)	0 (0%)
Multifocal	40 (35%)	7 (27%)
Unknown	12 (11%)	2 (8%)
Mean no. of biopsies sampled for detection of dysplasia (±SD)	12 (±11)	14 (±12)
Primary sclerosing cholangitis	14 (12%)	2 (8%)
Duration of follow-up (mo)	71 [0-209]	54 [0-111]

IBD, inflammatory bowel disease; LGD, low-grade dysplasia; IND, indefinite dysplasia.

Pathology Review

A total of 1547 histology slides from 87 patients were reviewed. The original diagnoses were flat LGD in 70 patients (80%) and IND in 17 patients (20%). Percentages of progression to advanced neoplasia in these 87 patients before histopathological review are shown in Table 2A. In 56 patients (64%), slides were discussed and reassessed by all three pathologists. Figure 3 shows the differences between the diagnoses after the first review by one expert pathologist and the diagnoses after assessment of the panel of pathologists. Overall, after review of the histological slides the number of confirmed flat LGD patients fell from 70 to 21. In 29 of these patients (41%) the diagnosis was downgraded to IND, in 17 (24%) no dysplasia could be detected at all, and in three flat LGD was found to be not related to the underlying IBD. Review of the flat IND cases resulted in a decrease of confirmed flat IND to 10 (59%). In three flat IND patients (18%) no dysplasia could be detected after review. However, four patients were found to have flat LGD instead of flat IND. Overall, histopathological review reduced the number of flat LGD patients from 70 to 25, but increased the number of flat IND from 17 to 39 (Table 3). Characteristics of colitis patients in whom the diagnosis was changed were not found to differ from patients in whom the diagnosis was confirmed. However, in the biopsies from LGD patients in whom the diagnosis was downgraded to "no dysplasia" or "IND," severe inflammation was more frequently encountered than in patients in whom the LGD diagnosis remained the same after review by the expert panel (50% versus 10%, $P < 0.01$).

Progression of Flat LGD to Advanced Neoplasia After Review

After reviewing all histological slides showing dysplasia or CRC, 11 of 25 flat LGD patients developed advanced neoplasia (44%) during a median follow-up time of 24

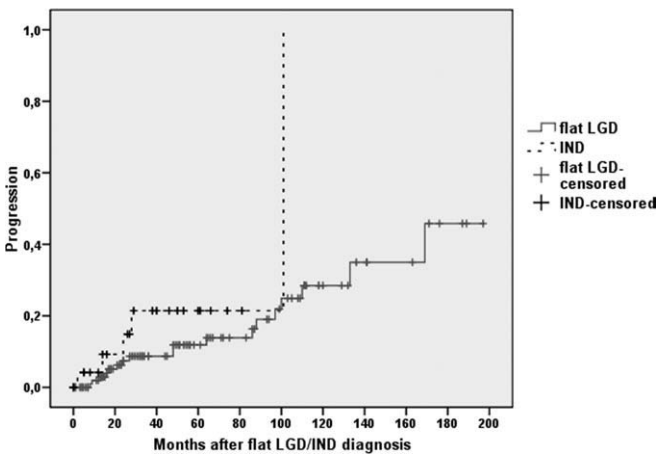

FIGURE 2. Kaplan–Meier curve comparing the progression rate to advanced neoplasia in patients with flat LGD and IND (log-rank test $P = 0.079$) before pathology review. Patients with no progression are censored at the moment of their last colonoscopy or colectomy. Vertical lines represent events of advanced neoplasia. LGD, low-grade dysplasia; IND, indefinite dysplasia.

TABLE 2. Development of Advanced Neoplasia in Patients with Flat LGD and IND Before (A) and After (B) Histopathological Review of the Diagnosis

	A. Before Review		B. After Review	
Variable	FLAT LGD $N = 70$	IND $N = 17$	FLAT LGD $N = 25$	IND $N = 39$
Advanced neoplasia during follow-up	13 (19%)	4 (24%)	11 (44%)	3 (8%)
HGD	3 (23%)	2 (50%)	4 (36%)	0 (0%)
HGD with concurrent CRC	2 (15%)	1 (25%)	3 (27%)	1 (33%)
HGD with subsequent CRC	4 (31%)	1 (25%)	3 (27%)	1 (33%)
CRC	4 (31%)	0 (0%)	1 (9%)	1 (33%)
Median time to progression (range)	27 [1-169]	21 [2-101]	24 [1-102]	133 [37-169]

LGD, low-grade dysplasia; IND, indefinite dysplasia; HGD, high-grade dysplasia; CRC, colorectal cancer.

months (range, 2–102) (Table 2B). Eight patients were diagnosed with UC (73%), one with CD (9%), and two with IC (18%). The advanced neoplasia was classified as HGD in four patients (36%), as HGD with concurrent CRC in three patients (27%), as HGD with subsequent CRC in three patients (27%), and as a single CRC in one patient (9%). From the 11 flat LGD cases that developed advanced neoplasia, seven had advanced neoplasia detected during colonoscopy and four had advanced neoplasia detected during colectomy. In one of the latter, HGD was found in the specimen of the colectomy that was performed 1 month after the detection of multifocal flat LGD. In the other three patients the indications for colectomy (performed 100, 101, and 35 months after flat LGD detection, respectively) were a villous lesion containing LGD, repeated multifocal flat LGD during colonoscopy and a stenosis in the sigmoid.

Overall, the rate of progression to advanced neoplasia in patients with a confirmed flat LGD diagnosis was found to be 37% at 5 years (95% CI, 0.16–0.58), compared to 16% at 5 years (95% CI, 0.05–0.26) in these patients before histopathological review (Fig. 4). This rate was not statistically significantly different between UC and CD patients ($P = 0.11$). The incidence rate for advanced neoplasia for all patients with a confirmed flat LGD diagnosis was 13.1 per 100 person years at risk.

Progression of Flat IND to Advanced Neoplasia After Review

After review of the histological slides, four patients with a confirmed diagnosis of flat IND developed LGD during follow-up. Of these, two progressed to HGD and CRC. In the whole group of 39 patients with a confirmed

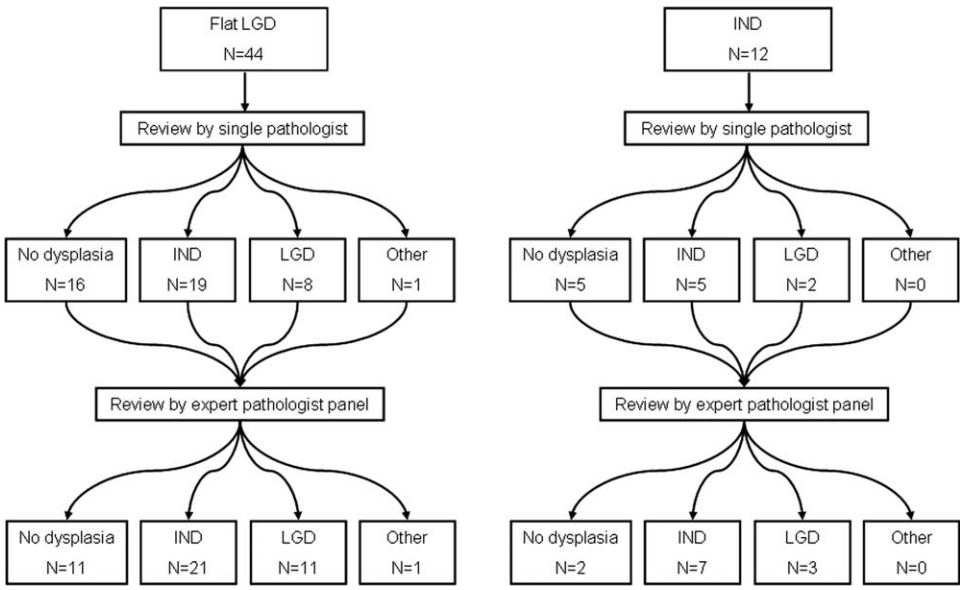

FIGURE 3. Flowchart of diagnoses of 44 flat LGD and 12 IND patients after review by one expert pathologist and after assessment of the panel of pathologists.

TABLE 3. Results of Histopathological Review of Histological Slides from 70 Flat LGD Patients and 17 Flat IND Patients

	Diagnosis After Histopathological Review				
Original Diagnosis	No Dysplasia	IND-PN	IND-PP	LGD	Other
70 flat LGD	17 (24%)	19 (27%)	10 (14%)	21 (30%)	3 (4%)
17 flat IND	3 (18%)	5 (29%)	5 (29%)	4 (24%)	0 (0%)

IND-PN, indefinite dysplasia, probably negative; IND-PP, indefinite dysplasia, probably positive; LGD, low-grade dysplasia.

diagnosis of flat IND, three UC patients (8%) developed advanced neoplasia during a median follow-up time of 133 months (range, 37–169) (Table 2B). IND was classified as "probably positive" in two of these patients and as "probably negative" in the other. All three patients progressed to CRC. From the three IND patients that developed advanced neoplasia, two had advanced neoplasia detected during colonoscopy. In one patient, CRC was detected in the specimen of a colectomy that was performed 133 months after the flat LGD diagnosis because of an LGD-bearing adenoma.

In the group of 36 IND patients that showed no progression to advanced neoplasia, IND was classified as "probably positive" in 15 patients (42%) and as "probably negative" in 21 patients (58%). Overall, the rate of progression to advanced neoplasia in patients with a confirmed flat IND diagnosis was 5% at 5 years (95% CI, 0–0.15), compared to 21% at 5 years (95% CI, 0–0.43) in these patients before histopathological review (Fig. 5). The incidence rate for advanced neoplasia for patients with a confirmed IND diagnosis was 2.4 per 100 person-years at risk.

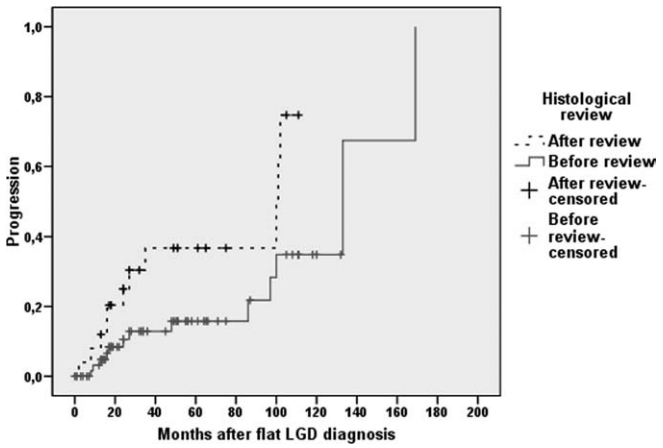

FIGURE 4. Kaplan–Meier curve comparing the progression rate to advanced neoplasia in patients with flat LGD before and after histopathological review (log-rank test $P < 0.05$). Patients with no progression are censored at the moment of their last colonoscopy or colectomy. Vertical lines represent events of advanced neoplasia. LGD, low-grade dysplasia.

Patients with No Dysplasia After Review

Of the 87 patients with flat LGD or flat IND, 20 patients (23%) were downgraded to "no dypslasia" after review of the histological slides (Table 3). None of these patients developed LGD during follow-up. One patient (5%) developed an adenomatous lesion with HGD that appeared to harbor CRC in the colectomy specimen. Originally, this patient was reported to have a focus of flat LGD 2 years previously. Histopathological review could not confirm the presence of LGD in this focus. None of the other patients that were downgraded to "no dysplasia" developed HGD or CRC during follow-up.

Risk Factors of Neoplastic Progression

After univariate and multivariate analysis of potential factors associated with neoplastic progression in patients with flat LGD or IND, no independent predictors for progression to advanced neoplasia were identified. Multifocal dysplasia was found to be a predictor of neoplastic progression in the univariate analysis, but after multivariate testing this was not confirmed (data not shown).

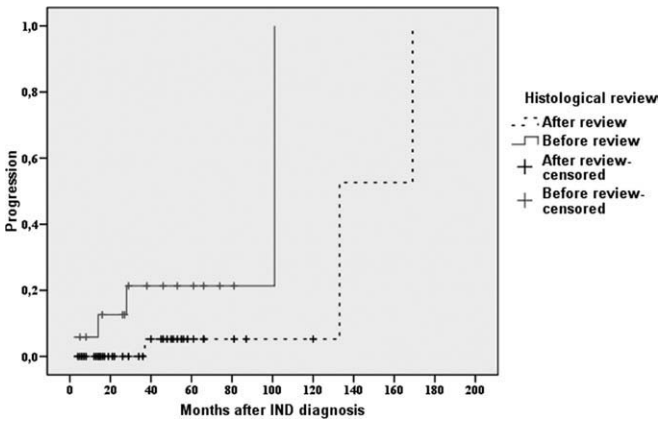

FIGURE 5. Kaplan–Meier curve comparing the progression rate to advanced neoplasia in patients with IND before and after histopathological review (log-rank test $P < 0.05$). Patients with no progression are censored at the moment of their last colonoscopy or colectomy. Vertical lines represent events of advanced neoplasia. IND, indefinite dysplasia.

DISCUSSION

This study demonstrates that a diagnosis of LGD in patients with IBD largely depends on the interpretation of the consulting pathologist. Furthermore, the study demonstrates that thorough histological classification of dysplasia can significantly improve the predictive value of LGD with regard to the development of advanced neoplasia. We found remarkable differences in both the numbers of flat LGD and IND patients and the progression rates associated with these diagnoses before and after histopathological review by expert pathologists. Based on the original pathology reports, the 5-year progression rate to advanced neoplasia in 113 patients with flat LGD was found to be 12%. Remarkably, this was lower than the 5-year progression rate in 26 IND patients (21%). After histopathological review we found that the 5-year progression rate to advanced neoplasia in the remaining 25 patients with flat LGD had increased to 37%, whereas the 5-year progression rate in 39 patients with IND had decreased to only 5%. Moreover, 20 patients with an initial diagnosis of flat LGD or IND were downstaged to "no dysplasia."

We did not identify clinical or pathological factors that were associated with the risk of progression. Although multifocal dysplasia seemed to be a predictor of progression in the univariate analysis, this did not reach significance in multivariate analysis. This may be due to the relatively low numbers of patients with confirmed LGD available for Cox analysis after histopathological review. Mesalazine treatment has been suggested to exert chemoprotective effects in longstanding colitis patients, although this is solely based on data from retrospective studies.[14–16] We were not, however, able to assess the contribution of drug-related parameters in the current analysis, as we were confronted with a high percentage of missing data regarding medication use.

In previous studies, conflicting data with respect to the clinical course of flat LGD have been reported ranging from no increased progression to 5-year progression rates of more than 50%. Compared to prior data reported by Ullman et al,[10] flat LGD patients in this study had more extensive disease, were more frequently suffering from PSC, and had a longer duration of follow-up. In spite of an apparently more severe phenotype in our study and the absence of histopathological confirmation by a second expert pathologist in the Ullman et al study, the 5-year progression rate of flat LGD was lower in our series. Whether differences in mesalazine prescription or other risk factors might have played a role in this respect is a matter of speculation. Another high progression rate was reported by Connell et al.[8] In that study the histopathological diagnosis was reviewed, but the progression rate was based on only nine patients. Both Connell et al and Ullman et al reported progression rates for UC patients only. Our study included both UC and CD patients. As the inflammation-dysplasia-carcinoma sequence is thought to be the pathogenetic denominator of CRC in both subgroups, we feel that inclusion of UC and CD patients is justified and that this does not explain the lower progression rates in our study. In contrast, in 60 patients with flat LGD included in the study of Befrits et al,[7] only two progressed to advanced neoplasia (HGD). In that study the diagnoses were made by two expert pathologists, but they refrained from use of the IND category, which may have led to a higher percentage of patients upgraded to LGD. Pekow et al[17] included this category and found a higher incidence rate for advanced neoplasia in patients with IND confirmed by two expert pathologists compared to patients with flat LGD. However, that study suffered from low patient numbers in both groups, which may have influenced the results. Histopathological review of the IND diagnoses in our study revealed a 5-year progression rate of only 5% for patients with IND. This low risk of progression is in line with several other, previously published studies.[18,19]

The mean number of biopsies per colonoscopy was rather low in our study (12 and 14 for LGD and IND, respectively). This was due to the fact that all cases of LGD or IND identified were included in the study, starting from the late 1980s until a few years ago. Thus, biopsies from both surveillance endoscopies and colonoscopies for other indications were used, resulting in a lower mean number of biopsies than guidelines generally advise.[20,21]

This might have resulted in sampling errors and thereby in an underestimation of the presence of multifocal LGD or synchronous flat HGD. However, since most cases of advanced neoplasia can easily be identified endoscopically, the effect of this phenomenon on our results is probably small.

All original pathology reports used in this study were produced by pathologists working in one of six university medical centers in the Netherlands. Histological slides from 87 patients in three university medical centers were reviewed for this study. The selection of centers for histopathological review was based on the availability of histological slides from these centers. To our knowledge, no differences exist between the patient populations of the six tertiary referral centers included in this study. Baseline progression rates (i.e., before histopathological review) of the 87 patients of whom histological slides were reviewed for this study were not significantly different from the progression rates of the total population of 139 (data not shown). Our objective was to assess a potential discrepancy in progression rates of flat LGD and IND before and after review by a panel of expert GI pathologists. This panel of expert pathologists was able to significantly better distinguish patients at an increased risk and patients at no or low risk for progression to advanced neoplasia. The total number of

patients with a diagnosis of flat LGD decreased, while confirmed LGD lesions displayed an increased progression rate to advanced neoplasia. As could be expected, the reverse phenomenon was encountered in patients with confirmed IND, a diagnosis characterized by epithelial changes not significant enough to be classified as LGD. Twenty patients were downgraded to "no dysplasia," of which all but one showed no development of any neoplasia during follow-up.

The large discrepancy in this study between the total number of patients with LGD before and after histological review reflects the poor interobserver agreement for dysplasia, which is a well-known phenomenon in literature.[11,12] In a study by Lim et al,[22] LGD slides from 40 patients were reviewed by five specialist GI pathologists. A consensus diagnosis, defined as agreement between at least three of five pathologists, was reached in 15 of 40 cases (38%), which is in line with our results. Although the present study focuses on academic hospitals where slides are often assessed by dedicated GI pathologists, we do not expect other outcomes if the study would have been performed in general hospitals, since agreement has been shown to be not significantly better between expert pathologists.

The management of patients with flat LGD remains a challenge. No consistent policy exists for the treatment of flat LGD; either intensification of the surveillance program or a proctocolectomy is recommended.[6,10,23] The differences in progression rates of flat LGD before and after histopathological review in this study leave room for doubt regarding the progression rates reported in previous studies that did not perform a methodical histopathological review of the histopathological slides. In our opinion, every histological slide with (a suspicion of) dysplasia should be reviewed by a panel of expert pathologists. In clinical practice this may cause a logistic problem, and therefore we would opt for a review by at least one expert GI pathologist who, in case of doubt, forwards the slide to an expert panel. Obviously, one cannot rely on the histopathological diagnosis of dysplasia alone. The large discrepancy between the number of flat LGD patients before and after histopathological review and the fact that not all flat LGD patients develop advanced neoplasia stresses the importance of identifying other characteristics that reliably identify patients at an increased risk of CRC.

In conclusion, this study indicates that patients with a *confirmed* diagnosis of flat LGD are at a significant increased risk of developing HGD or CRC, whereas patients with IND carry a low risk. This has great implications for clinical decision making in colitis patients with LGD. Although histopathological review by a team of dedicated pathologists increases the value of LGD as a predictive parameter, as shown in the present study, its use in daily practice might be hampered by logistics and costs and time constraints. Unfortunately, we were not able to identify other clinical parameters reliably predicting the development of advanced neoplasia in these patients. Evaluation of the use of potentially interesting biomarkers, such as p53, might provide valuable additional tools in this respect.

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