Increased risk of high-grade dysplasia and colorectal cancer in inflammatory bowel disease patients with recurrent low-grade dysplasia (CME)

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Background and Aims: The impact of recurrent low-grade dysplasia (LGD) on the risk of advanced neoplasia (high-grade dysplasia and colorectal cancer) in inflammatory bowel disease (IBD) patients is unknown. In addition, it is unclear how a neoplasia-free period after index LGD impacts this risk. We aimed to determine whether recurrent LGD is a risk factor for advanced neoplasia development and to evaluate the impact of a neoplasia-free time period after initial LGD diagnosis on the advanced neoplasia risk.

Methods: This is a nationwide cohort study using data from the Dutch National Pathology Registry to identify all IBD patients with LGD and ≥1 follow-up colonoscopy between 1991 and 2010 in the Netherlands. Follow-up data were collected until January 2016. We compared the cumulative advanced neoplasia incidence between patients with and without recurrent LGD at first follow-up colonoscopy using log-rank analysis. We subsequently studied the impact of a neoplasia-free period after initial LGD on the advanced neoplasia incidence.

Results: We identified 4284 IBD patients with colonic LGD with a median follow-up of 6.4 years. Recurrent LGD was a risk factor for advanced neoplasia (hazard ratio, 1.66; 95% confidence interval, 1.22-2.25; $P = .001$). A neoplasia-free period of at least 3 years after LGD protected against advanced neoplasia.

Conclusions: Recurrent LGD at follow-up colonoscopy after initial LGD was a risk factor for advanced neoplasia. A neoplasia-free period of at least 3 years after initial LGD was associated with a reduced subsequent risk of advanced neoplasia. (Gastrointest Endosc 2020;91:1334-42.)

Patients with inflammatory bowel disease (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC), bear an increased colorectal cancer (CRC) risk.[1] The main driver of CRC in IBD patients is chronic inflammation of the colonic tissue, which may lead to the development of a dysplastic precursor lesion. Subsequently, this lesion may eventually progress through different grades of dysplasia, including indefinite for dysplasia, low-grade dysplasia (LGD), and high-grade dysplasia (HGD) into CRC.[2] To detect and remove LGD before it progresses to advanced neoplasia (HGD and/or CRC), surveillance colonoscopies are recommended by national and international guidelines. For example, the surveillance guideline of the British Society of Gastroenterology sets the surveillance intervals at 1, 3, or 5 years depending on the patient's risk profile (low, medium, or high).[3]

Abbreviations: CD, Crohn's disease; CI, confidence interval; CRC, colorectal cancer; HGD, high-grade dysplasia; HR, hazard ratio; IBD, inflammatory bowel disease; IQR, interquartile range; LGD, low-grade dysplasia; PALGA, Dutch National Pathology Registry; ROC, receiver operating characteristic; UC, ulcerative colitis.

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IBD patients with a history of colonic LGD have a high advanced neoplasia risk estimated at 20% to 30% and are therefore considered high-risk patients.[4-6] Consequently, the British Society of Gastroenterology recommends annual surveillance colonoscopies during 5 consecutive years after LGD diagnosis. The surveillance interval may be extended if no dysplasia is detected at these 5 follow-up colonoscopies.[3] Similarly, the American Society for Gastrointestinal Endoscopy and the American Gastroenterological Association guidelines recommend an intensified surveillance strategy after LGD detection, without specifying the duration of this strategy.[7-9] The issue is that robust evidence supporting this intensive surveillance strategy after LGD diagnosis is absent. For example, it is unclear whether subsequent colonoscopies without recurrent or persistent neoplasia puts the patient in a lower-risk category. This is of major importance because frequent surveillance colonoscopies put a high burden on IBD patients and have a major impact on endoscopy capacity. Moreover, the impact of recurrent dysplasia on the advanced neoplasia risk is unknown, and the only available studies are small and reported conflicting results.[4,10] As such, the optimal surveillance strategy in IBD patients with LGD remains under debate.

In the current study, we aimed to determine the impact of recurrent/persistent LGD (termed as "recurrent dysplasia" going forward) on the advanced neoplasia risk in IBD patients with a history of LGD and to evaluate the impact of a neoplasia-free time period after initial LGD diagnosis on advanced neoplasia risk. To this end, we used a previously established nationwide cohort of IBD patients with a history of LGD in the Netherlands.[6]

METHODS

Study design

We studied the impact of recurrent LGD and a neoplasia-free period after LGD on the subsequent advanced neoplasia (HGD and CRC) risk in a retrospective Dutch nationwide IBD cohort with a history of LGD.

Study population

We used the nationwide network and registry of histopathology and cytopathology in the Netherlands (the Dutch National Pathology Registry [PALGA]) to identify our study population.[11] The database was searched for IBD patients with neoplasia (indefinite for dysplasia, LGD, HGD, and CRC) in the Netherlands between 1991 and 2010. Follow-up data were collected until January 2016, allowing long-term follow-up. The search terms have been described in detail in our previous publication.[6]

Inclusion and exclusion criteria

All patients with colonic IBD (CD, UC, and IBD unclassified) with LGD in the colon from January 1991 to December 2010 were included in this study. In previous studies we verified that PALGA is able to identify 95% of IBD patients in hospitals in the Netherlands and that an IBD diagnosis in the PALGA database accurately corresponds with an IBD diagnosis in the patient's medical charts.[6,12] Exclusion criteria were dysplasia before a diagnosis of IBD, HGD, or CRC before LGD development; lack of $\geq$1 follow-up report after initial LGD; (sub)total colectomy before LGD; and patients with hereditary CRC syndromes.

Data collection

Both baseline demographics and data regarding colorectal neoplasia were extracted from PALGA. Baseline characteristics included gender, type of IBD diagnosis, date and type of colonic resections, and age at first LGD. In addition, we extracted the date and type of neoplasia and the date of colonoscopies. We did not enter age at IBD diagnosis as a variable in our analysis because the PALGA data set does not contain a specific entry allowing unambiguous extraction of this outcome.[6] The first neoplastic lesion with LGD was defined as the index LGD. Histopathologic follow-up reports (including the reports of surgical resection specimens) were evaluated for development of subsequent LGD, HGD, or CRC. Recurrent dysplasia was defined as LGD >6 months after index LGD. Follow-up colonoscopies were defined as colonoscopies after the index LGD, irrespective of the indication. A negative follow-up colonoscopy was defined as a colonoscopy without LGD or advanced neoplasia.

IBD surveillance strategy in the Netherlands

In the 1990s surveillance colonoscopies in IBD patients were performed using standard-definition white-light endoscopy with targeted biopsy sampling of abnormalities in combination with random biopsy sampling. Subsequently, high-definition white-light endoscopy became the mainstay endoscopic technique between 2005 and 2010. After updates in IBD surveillance guidelines in 2008, Dutch centers gradually adopted chromoendoscopy as a first-choice modality for IBD surveillance.[13] Chromoendoscopy involves pancolonic dye-spraying using either indigo carmine or methylene blue, along with targeted biopsy sampling of abnormal areas. The interval between surveillance colonoscopies is based on the guidelines of the British Society of Gastroenterology.[3]

Statistics

Impact of recurrent LGD on advanced neoplasia. To determine the impact of recurrent LGD on the risk of advanced neoplasia, we selected patients with 2 or more follow-up colonoscopies and compared the cumulative incidence of advanced neoplasia between patients with and without recurrent LGD at the first follow-up colonoscopy using Kaplan Meier curves and log-rank analysis. Only patients who had undergone a first follow-up

colonoscopy within a maximum of 3 years after the index LGD were included in this analysis to reduce heterogeneity. The time to event was calculated from the first colonoscopy after the index LGD until advanced neoplasia or end of follow-up. End of follow-up was defined as the last follow-up colonoscopy or (sub)total colectomy, given the low CRC risk after colectomy.[14] Because several risk factors may impact the advanced neoplasia risk, we performed a multivariable Cox analysis adjusting for these previously identified and published risk factors (ie, male gender, diagnosis of index LGD in an academic center, and diagnosis of index LGD ≥55 years).[6] Moreover, improved endoscopic techniques and guidelines over time may impact the advanced neoplasia risk as well. Therefore, we included the year of dysplasia diagnosis (categorized as 1990-1994, 1994-1999, 2000-2004, 2005-2010) as a confounder in our Cox model. Finally, incidence rates were calculated per 1000 patient-years of follow-up.

Impact of a neoplasia-free period after index LGD on advanced neoplasia. For our second aim, we assessed how a neoplasia-free period after the index LGD impacts the risk of advanced neoplasia. We performed the following 3 steps:

1. Evaluate whether a longer neoplasia-free period after the index LGD resulted in a lower subsequent risk of advanced neoplasia
2. Determine the optimal cutoff point of the length of the neoplasia-free period
3. Verify in our cohort if patients who were neoplasia free for this period indeed had a low subsequent risk of advanced neoplasia

Evaluate whether a longer neoplasia-free period after the index LGD resulted in a lower subsequent risk of advanced neoplasia. The area under the receiver operating characteristic (ROC) curve was applied to evaluate the prognostic impact of the length of the neoplasia-free time period in predicting advanced neoplasia development. For this analysis, we used the clinically relevant outcome of advanced neoplasia development within 10 years of the index LGD. Therefore, only patients with a minimum of 10 years of follow-up or those who developed advanced neoplasia within 10 years were included. To verify the prognostic impact of a longer neoplasia-free period, we calculated the maximum neoplasia-free time for each patient. The maximum neoplasia-free time is defined as the time from LGD diagnosis until the last negative follow-up colonoscopy within a time interval of 10 years.

Determine the optimal cutoff point of the length of the neoplasia-free period. After confirmation of the prognostic impact of the length of the neoplasia-free time period, the optimal cutoff value of the neoplasia-free period for the risk of advanced neoplasia was determined from the ROC curve. Ideally, this cutoff point corresponds to a neoplasia-free time period that is followed by a low advanced neoplasia risk, whereas the number of unnecessary surveillance colonoscopies is limited. Therefore, we choose the cutoff point with the most optimal sensitivity × specificity. Because a high sensitivity corresponds to a low risk of missing advanced neoplasia, we choose a cutoff value with a sensitivity of at least 85%. A high specificity corresponds with a low number of unnecessary colonoscopies.

Verification of the identified cutoff point. We verified the optimal cutoff value (referred to as x years) established in the ROC curve in the total cohort of IBD patients with LGD. We used a Kaplan-Meier plot to illustrate the cumulative incidence of advanced neoplasia in the total cohort of IBD patients who had a neoplasia-free follow-up period of at least x years after the index LGD. In addition, we analyzed the cumulative incidence of any neoplasia (ie, LGD or advanced neoplasia). Time to event was calculated from moment of cutoff (ie, date of index LGD + x years) to event or to censoring. Patients with advanced neoplasia at the first colonoscopy that was performed more than x years after the index LGD were excluded because most of these patients may already have had advanced neoplasia at the moment of cutoff (but not yet detected because colonoscopy was performed later than the cutoff point). Additionally, we performed a sensitivity analysis including these patients (worst-case scenario) and a sensitivity analysis including patients without previously identified risk factors for advanced neoplasia development (best-case scenario).

Risk of recurrent dysplasia and advanced neoplasia after sporadic adenomas. We evaluated the risk of recurrent dysplasia and advanced neoplasia after sporadic adenomas. In clinical practice, the distinction between colitis-associated neoplasia and sporadic adenoma is often not clear.[15] In general, lesions are categorized as sporadic adenomas if they are located in historically noninflamed colonic segments.[16] Therefore, we assessed whether there was any histologic inflammation in the colonic segment that harbored the dysplastic lesion simultaneously or before the moment of dysplasia detection. For this purpose, we analyzed all individual pathology reports of the subgroup of patients who developed LGD in the most recent 5 years of the inclusion period (2005-2010). We compared the cumulative incidence of recurrent LGD and advanced neoplasia using log-rank test.

General statistics. Outcomes with a normal distribution were presented as means with standard deviation, and non-normally distributed outcomes were presented as medians with interquartile range (IQR). The proportional hazards assumption was tested by testing time–covariate interactions and visual inspection of log-minus-log plots. A $P < .05$ was considered statistically significant. SPSS Statistics (IBM, version 25, IBM, Armonk, NY, USA) was used for statistical analyses.

TABLE 1. Baseline characteristics of included IBD patients with LGD (n = 4284)

Characteristic	Value
Male gender	2630 (61.4)
Disease	
Ulcerative colitis	3065 (71.5)
Crohn's disease	970 (22.6)
IBD unclassified	249 (5.8)
Age at LGD, y	55.3 ± 14.8
Median follow-up after dysplasia, y	6.4 (3.2-11.3)
Follow-up after IBD diagnosis, y	13.8 ± 8.2
Recurrent LGD	1620 (37.8)
Two or more follow-up colonoscopies	2788 (65.1)

Values are n (%), mean ± standard deviation, or median (interquartile range).
IBD, Inflammatory bowel disease; *LGD*, low-grade dysplasia.

Ethics

The study was approved by the PALGA Ethical Committee (lzv-1215) and Institutional Review Board on February 27, 2017.

RESULTS

Patient selection

The PALGA search yielded 4284 IBD patients with LGD available for inclusion. The results of the PALGA search has been described in detail in a prior publication.[6] Of these 4284 patients, 1620 patients (37.8%) developed recurrent LGD after a median of 3.6 years (IQR, 1.7-6.9) after the index LGD. Baseline characteristics of all included IBD patients with LGD are shown in Table 1. Of 4284 patients, 3065 (71.5%) had UC, 970 (22.6%) CD, and 249 (5.8%) IBD unclassified. The median follow-up was 6.4 years (IQR, 3.2-11.3). During follow-up, patients underwent a median of 5 colonoscopies. The median time between colonoscopies was 1.4 years (IQR, .8-2.3). Of 4284 patients, 551 (12.9%) underwent (sub)total colectomy.

Recurrent versus no recurrent LGD

Recurrent LGD. A total of 2788 patients had 2 or more follow-up colonoscopies (2040 UC, 584 CD, and 164 IC). Of these, 2047 patients (73%) received a follow-up colonoscopy within 3 years after the index LGD and were therefore included in this analysis (Fig. 1). Recurrent LGD at this first follow-up colonoscopy was detected in 392 of 2037 patients (19.1%), of whom 56 patients eventually developed advanced neoplasia (14.3%, 30 CRC and 26 HGD) during 2467 person-years of follow-up. By contrast, only 166 of 1655 patients without recurrent LGD at the first follow-up colonoscopy developed advanced neoplasia (10.0%, 111 CRC, 55 HGD) in 11,832 person-years. The incidence rate of advanced neoplasia was 22.7 per 1000 patient-years in patients with recurrent LGD versus 14.0 per 1000 patient-years in patients without recurrent LGD. Patients with recurrent LGD had a higher cumulative incidence rate of advanced neoplasia compared with patients without recurrent LGD (log-rank, hazard ratio [HR], 1.66; 95% confidence interval [CI], 1.22-2.25; $P = .001$) (Fig. 2). The 10-year cumulative incidence of advanced neoplasia was 17.4% and 12.2% in patients with recurrent and no recurrent LGD, respectively.

Our multivariable analysis showed that recurrent LGD remained an independent risk factor for advanced neoplasia after correction for the confounders age, academic center, male gender, and year of LGD diagnosis (HR, 1.56; 95% CI, 1.15-2.11; $P = .005$).

Neoplasia-free time after index LGD. In total, 1444 patients (1060 UC, 287 CD, 97 IBD unclassified) had a follow-up period of at least 10 years or developed advanced neoplasia within 10 years. For this subgroup, the association between the number of patients developing advanced neoplasia and maximum neoplasia-free time after the index LGD is shown in Figure 3A. The value 0 represents patients with new neoplasia at the first follow-up colonoscopy and hence a neoplasia-free follow-up period of 0 years. Based on these results a ROC curve was constructed that showed an area under the ROC curve of .76 (95% CI, .74-.79; $P < .001$) (Fig. 3B). Therefore, neoplasia-free time can be considered a fair predictor for risk of advanced neoplasia development. A cutoff value of 3 years of neoplasia-free time after the index LGD was associated with a sensitivity and specificity of 89.3% (95% CI, 85.9%-92.1%) and 55.1% (95% CI, 52.0%-58.2%), respectively, for detecting advanced neoplasia.

Figure 4 illustrates the cumulative incidence of advanced neoplasia in the total group of 2383 patients (1715 UC, 524 CD, 144 IBD unclassified) who remained neoplasia-free for 3 years after the index LGD. The *x*-intercept represents the moment the cutoff of a neoplasia-free period of 3 years was reached, thus the date of index LGD + 3 years. The subsequent 3- and 5-year cumulative incidences were, respectively, .9% and 2.2% for advanced neoplasia and 19.8% and 29.5% for any dysplasia (ie, LGD + advanced neoplasia) (Supplementary Fig. 1, available online at www.giejournal.org). The incidence rate of advanced neoplasia was 8.5 per 1000 patient-years (CRC, 5.2/1000 patient-years). Patients without risk factors for advanced neoplasia development (male gender, diagnosis of index LGD in an academic center, and diagnosis of index LGD ≥55 years; best-case scenario) who remained neoplasia-free 3 years after the index LGD had an even lower risk of advanced neoplasia (incidence rate, 5.6/1000 patient-years; 3- and 5-year cumulative incidences of .5% and 1.4%; $P = .048$). In the sensitivity analysis (worst-case scenario, 77 additional IBD patients with advanced neoplasia at first follow-up >3 years after the index LGD included), the incidence rate of advanced neoplasia was 13.2 per 1000 patient-years.

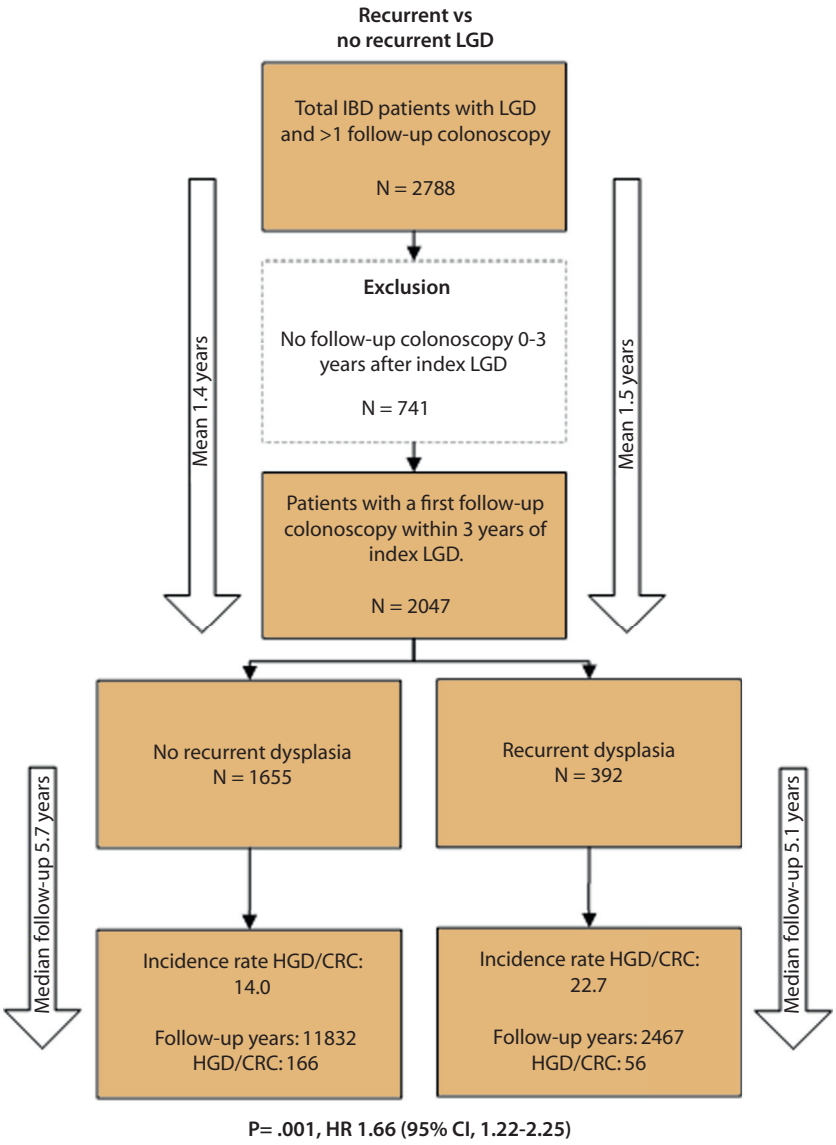

Figure 1. Risk of advanced neoplasia in patients with and without recurrent low-grade dysplasia (LGD) at first follow-up colonoscopy (within 3 years) after the index LGD. *IBD*, Inflammatory bowel disease; *HGD*, high-grade dysplasia; *CRC*, colorectal cancer; *HR*, hazard ratio; *CI*, confidence interval.

We then extrapolated our results to all patients who remained neoplasia-free at 3 years and would continue yearly surveillance until 5 years after index LGD. In that scenario, a total of 355 patients should be screened to find 1 additional case of advanced neoplasia (42 patients in the worst-case scenario).

Risk of recurrent neoplasia in sporadic adenomas in IBD

Based on the histopathology reports, 50.1% of patients had extensive colitis (extending proximal to the splenic flexure) and 40.3% had nonextensive disease. In 9.6% of patients, the specific colonic location of inflammation was not reported. The exact colonic location of the LGD was reported in 1064 of 1557 patients. We observed that 190 of 1064 patients (17.9%) had LGD in a colonic segment without documented inflammation, whereas 783 of 1064 patients (73.6%) had LGD in a colonic segment with reported histologic inflammation (in 91 of 1064 patients [8.5%] the exact location of colonic disease activity was never specified). We observed no differences in the risk of recurrent LGD (HR, 1.11; 95% CI, .85-1.45; $P = .44$) or of advanced neoplasia (HR, 1.58; 95% CI, .81-3.06; $P = .18$) between LGD located in an inflamed versus a noninflamed colonic segment.

DISCUSSION

In this nationwide study we found that recurrent LGD at follow-up colonoscopy after LGD is a risk factor for developing advanced neoplasia in IBD patients (incidence rate of 22.7 per 1000 patient-years for recurrent LGD vs 14.0

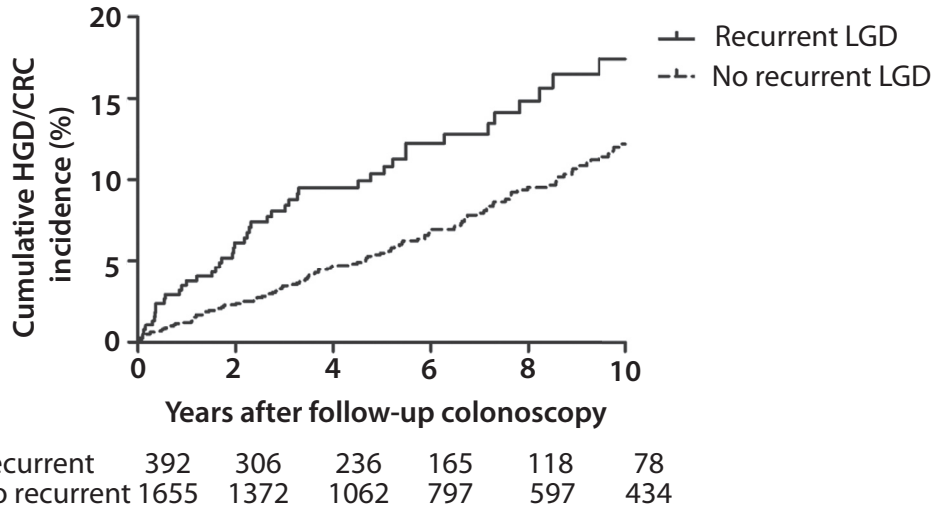

Figure 2. Kaplan-Meier plot showing the cumulative incidence of advanced neoplasia in IBD patients with recurrent and without recurrent low-grade dysplasia (LGD) at first follow-up colonoscopy after the index LGD. *IBD*, Inflammatory bowel disease; *HGD*, high-grade dysplasia; *CRC*, colorectal cancer.

per 1000 patient-years for no recurrent LGD). Second, we found that a neoplasia-free follow-up period of 3 years after the index LGD was associated with a reduced advanced neoplasia risk (incidence rate of 8.5/1000 patient-years). These results demonstrate the advanced neoplasia risk in IBD patients with LGD and may impact current surveillance guidelines.

Recurrence of LGD is a frequent finding in IBD patients with LGD. We found that 37.8% of patients with LGD developed recurrent LGD. This relatively high number is still lower than previously reported recurrence rates of LGD in a small cohort from 2002 (44/60, 73.3%).[17] Moreover, we found an increased advanced neoplasia incidence in patients with recurrent dysplasia. Likewise, in the general non-IBD screening population, patients with recurrent colorectal adenomas at first follow-up had a higher risk of developing advanced neoplasia at their second follow-up compared with patients with a negative first follow-up colonoscopy.[18,19] Robust data on advanced neoplasia risk in IBD patients with recurrent dysplasia are absent, and the available literature reported conflicting results. One study identified a history of indefinite for dysplasia before LGD as a risk factor for advanced neoplasia in 172 UC patients with LGD.[4] By contrast, a small study (n = 46) found no increased advanced neoplasia incidence in IBD patients with recurrent LGD.[10]

One could hypothesize that recurrent LGD occurs in the mucosa of IBD patients who underwent a larger field change of cancer-associated molecular alterations in the colon.[20] This concept of field cancerization assumes that there are multiple patches of premalignant mucosa with mutant clones close to the primary tumor. These mutant clones are histologically indistinguishable from the normal cell population but harbor the potential of tumor development.[21,22] Because these field changes are primed to develop multifocal (pre)cancerous changes, the presence of a larger field change might result in a higher CRC risk. Recurrent LGD may be the outcome of this field cancerization, which would explain the increased advanced neoplasia risk in these patients. However, the design of the current study did not allow the further testing of this hypothesis, and future studies are required to explore this theory.

Given the concept of field cancerization, one may hypothesize that patients with colitis-associated neoplasia bear an increased recurrent LGD and advanced neoplasia risk compared with IBD patients with sporadic adenomas. However, we observed a similar risk of recurrent LGD (HR, 1.11; 95% CI, .85-1.45; $P = .44$) and advanced neoplasia (HR, 1.58; 95% CI, .81-3.06; $P = .18$) between LGD located in an inflamed versus a noninflamed colonic segment. This is in line with prior cohort studies that reported no significant difference in risk of recurrent dysplasia after removal of a sporadic adenoma versus a colitis-associated adenoma (HR for colitis-associated dysplasia relative to sporadic adenoma, 1.3; 95% CI, .6-2.7; $P = .55$).[23-25] In addition, a study reported an increased risk of advanced neoplasia in Dutch IBD patients with a sporadic adenoma compared with non-IBD patients with a sporadic adenoma.[26] Moreover, 43.8% of IBD patients with untreated sporadic adenomas developed colitis-associated neoplasia in the same colonic segment.[27] These data suggest that the distinction between sporadic adenomas and colitis-associated dysplasia does not impact surveillance intervals, given the increased neoplasia risk in both IBD patients with a sporadic adenoma and IBD patients with colitis-associated dysplasia and the lack of clear definitions to distinguish colitis-associated neoplasia and sporadic adenomas.

The observation of a decreased cancer risk in patients with negative endoscopies accords with results coming

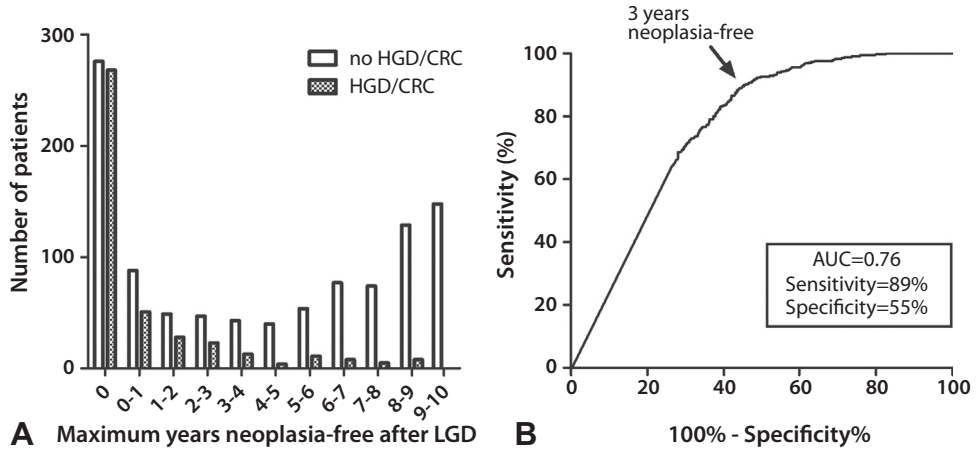

Figure 3. A, Inflammatory bowel disease patients (n = 1444) with at least 10 years of follow-up or advanced neoplasia within 10 years, illustrating the number of patients with and without advanced neoplasia within 10 years of the index LGD, stratified by maximum years of neoplasia-free time. **B,** Corresponding receiver operating characteristics curve. The *arrow* represents the cutoff value of 3 years. *LGD*, Low-grade dysplasia, *HGD*, high-grade dysplasia; *CRC*, colorectal cancer; *AUC*, area under the curve.

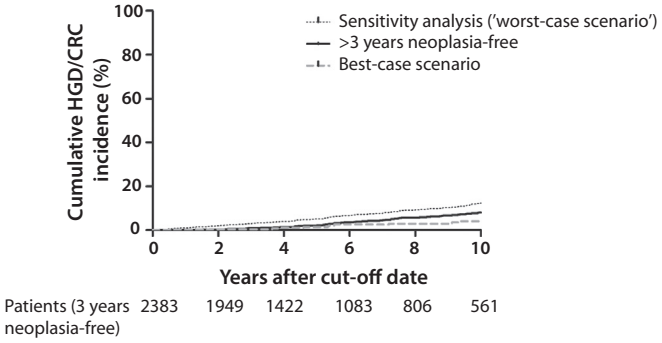

Figure 4. Kaplan-Meier plot showing the cumulative incidence of advanced neoplasia in the 2383 inflammatory bowel disease (IBD) patients with a neoplasia-free period of 3 years after the index low-grade dysplasia (LGD). The *x* intercepts represent the moment the neoplasia-free period reached the cutoff of 3 years (index LGD date + 3 years). The best-case scenario represents the group of patients with no risk factor (ie, not male gender, index LGD ≥55 years, or follow-up at an academic center). In the sensitivity analysis, 77 additional IBD patients with advanced neoplasia at the first follow-up >3 years after the index LGD were included. *HGD*, High-grade dysplasia; *CRC*, colorectal cancer.

from other cancer screening programs.[28] Recently, a multicenter retrospective analysis of low-risk IBD patients undergoing CRC surveillance reported a low advanced neoplasia risk in patients who had consecutive technically adequate colonoscopies without neoplasia and no other endoscopic abnormalities.[29,30] However, data regarding the impact of a neoplasia-free period in the high-risk category of IBD patients with LGD are not available. To date, only 1 small study reported that 6 of 15 IBD patients (40%) with a negative follow-up colonoscopy after LGD still developed recurrent LGD thereafter,[31] yet no study reported on the subsequent risk of advanced neoplasia. We found that a neoplasia-free period of 3 years after the index LGD was associated with a reduced subsequent incidence rate of advanced neoplasia of 8.5 per 1000 patient-years (CRC, 5.2/1000 patient-years). To put this into perspective, previous studies reported an average risk of advanced neoplasia in IBD patients with a history of LGD of 17 to 18 per 1000 patient-years.[5,6] In another high-risk category of IBD patients with concomitant primary sclerosing cholangitis, a higher incidence rate of advanced neoplasia of 13 per 1000 patient-years was reported.[32] However, the incidence rate of CRC of 5.2 per 1000 patient-years still exceeds the average risk in the general IBD population. A meta-analysis reported an incidence rate of CRC of .7 per 1000 patient-years in the first decade and 4.2 per 1000 patient-years after more than 20 years' disease duration in the general IBD population.[33]

Our results may impact current surveillance guidelines. The American Society for Gastrointestinal Endoscopy and American Gastroenterological Association guidelines recommend an increased surveillance strategy after LGD detection, without specifically stating the duration and frequency of this intensified strategy.[8,9] The British Society of Gastroenterology recommends performing yearly colonoscopy for 5 years after LGD detection.[3] Because dysplasia increased the advanced neoplasia risk in our study, our results underline the current intensified surveillance strategy after LGD detection including yearly surveillance. However, based on our data, 355 patients would have to undergo yearly surveillance after a neoplasia-free period of 3 years to detect 1 additional case of advanced neoplasia in the subsequent 2 years (ie, until 5 years after the index LGD). This risk was even lower in patients without previously identified risk factors and a subsequent neoplasia-free period of 3 years. This results in multiple negative endoscopies associated with a high burden for patients. Thus, our findings suggest that surveillance intervals may be extended if patients remain

neoplasia-free 3 years after LGD. In addition, patients with a baseline high-risk profile (eg, concomitant primary sclerosing cholangitis) may benefit from a prolonged annual surveillance strategy.[32] Future prospective studies are needed to further confirm these results and aid in risk stratification.

Strengths of our study include the nationwide study approach and the large size of our cohort with long-term follow-up. Our study also comes with some limitations. Inherent to the retrospective nature of our study, there were no standardized intervals between colonoscopies. This might have resulted in selection bias, because particularly patients who were considered at highest CRC risk might have received multiple follow-up colonoscopies. Second, although our results provide insight into the general advanced neoplasia risk in patients with LGD in a nationwide setting, no clinical and endoscopic data were available. Therefore, we could not correct for clinical confounders like endoscopic technique used, LGD location and morphology (ie, polypoid, nonpolypoid, and endoscopically invisible), treatment of dysplastic lesions (biopsy sampling or endoscopic removal), concomitant diseases such as primary sclerosing cholangitis, and the extent of inflammation. By contrast, our population-based approach results in data representative for the IBD population at large. Third, our cohort enrolled patients with LGD between 1991 and 2010, whereas current updated surveillance strategies, optimization of anti-inflammatory therapies, and new advanced endoscopic techniques may influence outcomes over time.[34,35] However, in our previous study we analyzed data from 2 different cohorts based on time of LGD (1991-2000 and 2000-2010) and did not detect significant differences. Moreover, we verified in our cohort that recurrent LGD remained a risk factor after correction for year of LGD diagnosis.

In conclusion, in this nationwide study we found that patients with recurrent LGD are at increased risk of developing advanced neoplasia compared with patients without recurrent dysplasia (HR, 1.66). In addition, a neoplasia-free period of 3 years after the index LGD reduced the advanced colonic neoplasia risk. Our results support current surveillance guidelines recommending yearly surveillance colonoscopy after the detection of LGD in IBD patients. However, our findings suggest that subsequent lengthening of the surveillance intervals could be considered in selected low-risk patients who remain neoplasia-free in the subsequent 3 years after LGD.

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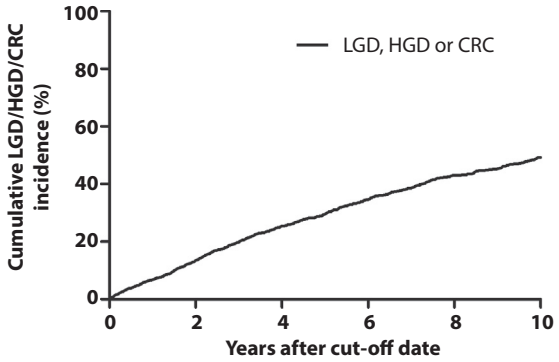

Supplementary Figure 1. *LGD*, Low-grade dyplasia; *HGD*, high-grade dysplasia; *CRC*, colorectal cancer.