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Clinical implications of low grade dysplasia found during inflammatory bowel disease surveillance: a retrospective study comparing chromoendoscopy and white-light endoscopy

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ABSTRACT

Background and study aims Current guidelines recommend the use of pancolonoscopic chromoendoscopy for surveillance of patients with inflammatory bowel disease (IBD). It is currently unknown whether low grade dysplasia (LGD) found using chromoendoscopy carries a similar risk of high grade dysplasia (HGD) or colorectal cancer (CRC) compared with LGD detected using white-light endoscopy (WLE). The aim of this study was to compare the risk of advanced neoplasia, a combined endpoint of HGD and CRC, during follow-up after detection of lesions containing LGD identified with either chromoendoscopy or WLE.

Patients and methods A retrospective cohort was established to identify patients who underwent IBD surveillance for ulcerative colitis or colonic Crohn's disease between 2000 and 2014. Subgroups were identified, based on the endoscopic technique (standard definition resolution WLE, high definition resolution WLE or chromoendoscopy). LGD detected in random biopsies was considered invisible LGD. Patients were followed until detection of advanced neoplasia, colectomy, death, or the last known surveillance colonoscopy.

Results Of 1065 patients undergoing IBD surveillance, 159 patients underwent follow-up for LGD, which was visible in 133 cases and invisible in 26 cases. On follow-up, five cases of HGD and five cases of CRC were detected. The overall incidence rate of advanced neoplasia was 1.34 per 100 patient-years with a median follow-up of 4.7 years and a median time to advanced neoplasia of 3.3 years. There were no significant differences in the incidence of advanced neoplasia between chromoendoscopy-detected and WLE-detected LGD.

Conclusion Advanced neoplasia was found to develop infrequently after detection of LGD in patients undergoing endoscopic surveillance for IBD. LGD lesions detected with either chromoendoscopy or WLE carry similar risks of advanced neoplasia over time.

Introduction

Patients with longstanding extensive ulcerative colitis (UC) or Crohn's colitis are at increased risk of developing colorectal cancer (CRC) [1]. Additional risk factors for the development of colitis-associated CRC are: a family history of CRC, early age of inflammatory bowel disease (IBD) onset, a concurrent diagnosis of primary sclerosing cholangitis (PSC), presence of post-inflammatory polyps, and ongoing disease activity [2, 3]. Recent studies have estimated that the cumulative risk of CRC in IBD patients is approximately 5% after a disease duration of 20 years or more [4, 5], which is lower than previously reported [6]. The occurrence of CRC is thought to be preceded by neoplastic progression via low grade dysplasia (LGD) and high

grade dysplasia (HGD) [7, 8], opening a window of opportunity for secondary prevention through surveillance colonoscopies.

Currently, high definition resolution (HDR) colonoscopy, if possible combined with pancolonoscopic dye-spraying (chromoendoscopy), is considered the most sensitive method for the detection of dysplasia in patients with colonic IBD [9]. This is based on evidence showing a higher dysplasia yield for chromoendoscopy than for standard definition resolution white-light endoscopy (SDR-WLE) [10–12]. It is, as of yet, unknown if lesions detected using HDR-WLE or chromoendoscopy indicate a similar risk of future advanced neoplasia, defined as HGD or CRC, to those detected by SDR-WLE. The aim of this study was therefore to compare the risk of developing HGD or CRC following the detection of lesions containing LGD during colonoscopic IBD surveillance using WLE and chromoendoscopy.

Patients and methods

Patient selection

Patients with IBD were retrospectively identified from three Dutch tertiary referral centers using diagnosis and treatment combinations, which resemble the World Health Organization (WHO) International Classification of Disease coding system [13]. Patients undergoing endoscopic surveillance between January 2000 and June 2014 were selected. Patients were considered eligible for colonoscopic surveillance if they had had a disease duration of at least 8 years and had involvement of at least 30% of the colonic mucosa. A concomitant diagnosis of PSC was considered an immediate indication for surveillance.

Patients' medical records were reviewed to retrieve demographic data, including IBD type, date of IBD diagnosis, maximum (endoscopic) disease extent, family history of CRC, and history of dysplasia before surveillance. In patients with Crohn's disease, the disease was categorized using the Montreal classification.

Endoscopic technique

Colonoscopies were classified as surveillance endoscopies when the endoscopy report explicitly stated this as the indication for the procedure and when a surveillance protocol included either WLE with random biopsies or the use of chromoendoscopy. At the start of the study period, surveillance colonoscopies were performed using WLE and involved targeted biopsies of any abnormality, along with a random biopsy protocol. Following updates in guidelines, all three participating centers gradually adopted chromoendoscopy as their first-choice modality for IBD surveillance [9]. Chromoendoscopy involves pan-colonic dye-spraying using either 0.1% methylene blue or 0.3% indigo carmine, along with targeted biopsy of abnormal areas.

Only endoscopists with extensive experience in surveillance of IBD patients performed chromoendoscopy. For each surveillance procedure, the type of colonoscope and the use of pan-colonic dye-spraying were retrieved from the endoscopy report. The colonoscope types were stratified based on image quality (SDR-WLE or HDR-WLE), as provided by the manufacturer.

The interval between surveillance colonoscopies was determined using the criteria stated in the updated guidelines of the British Society of Gastroenterology [9].

Detection of neoplasia

For each colonoscopic procedure, pathology reports were reviewed to identify cases with dysplastic lesions. For each lesion, additional data were collected on size, location, endoscopic morphology, histologic classification, p53 status, and endoscopic management. Patients were enrolled into the study following identification of their first LGD lesion during surveillance (hereafter called the index lesion). All LGD lesions identified through targeted biopsies were considered visible lesions.

The endoscopic technique employed to detect the index lesion was used to stratify the patients into HDR-WLE, SDR-WLE, or chromoendoscopy subgroups for follow-up. All chromoendoscopic colonoscopies were performed using HDR equip-

ment. If the index lesion was found in a random biopsy in the absence of a visible dysplastic lesion, the patient was allocated to a separate subgroup (invisible dysplasia). Lesions detected using random biopsies were considered to be non-resected. If an endoscopic procedure yielded multiple spatially distinct dysplastic lesions, this was considered to be multifocal dysplasia.

Incidence of advanced neoplasia during follow-up

All patients in whom an index lesion was identified were followed up until 1 July 2015. Patients were excluded from further analysis if no follow-up colonoscopy had taken place by this time or if the index lesion had been managed by colectomy rather than endoscopic follow-up.

The incidence of advanced neoplasia was defined as the presence of HGD or CRC, found either during colonoscopy or in a surgical colectomy specimen. Persistence of dysplasia was defined as the presence of LGD found during subsequent surveillance colonoscopies.

All colorectal cancers were coded according to the Dukes' classification. Censoring was performed in case of colectomy, death, or the last known surveillance colonoscopy before 1 July 2015.

Statistical analysis

Baseline data are presented for unique patients rather than for procedures. Dichotomous outcomes are presented as the number of events with a corresponding percentage and were compared using the chi-squared test. Continuous data are presented as a mean with standard deviation (SD) or median and range and were compared by the Student's *t* test or Mann-Whitney *U* test according to normality. Advanced neoplasia-free survival was examined using Kaplan-Meier curves and comparisons were made using Cox proportional hazard modeling. The risk of advanced neoplasia is presented as the number of events per 100 patient-years after identification of the index lesion.

Throughout the entire analysis, two-sided *P* values were set at 0.05 for identification of a statistically significant difference. All data analyses were performed using SPSS version 21 (IBM Corp., Armonk, New York, USA).

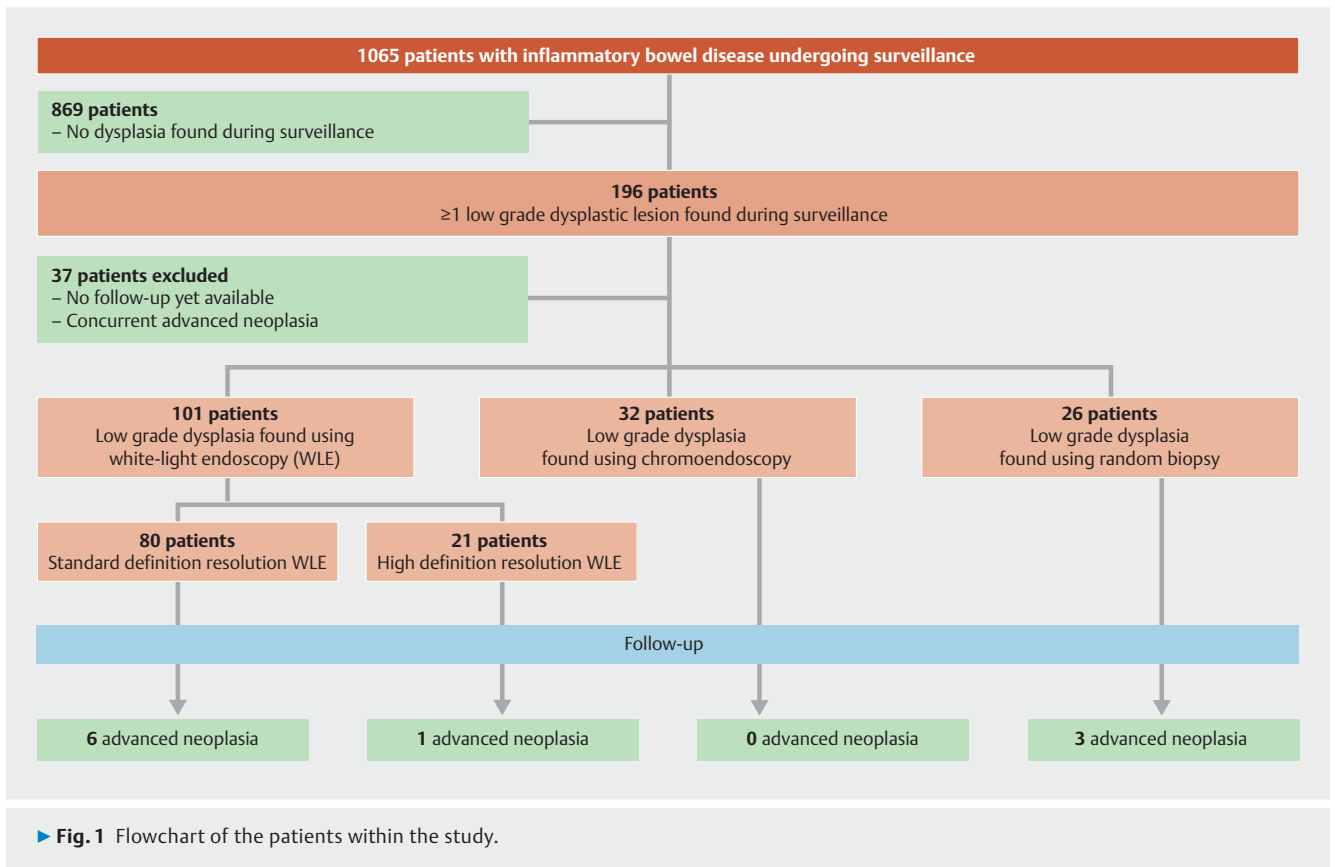
Results

Patient selection

Of 1065 patients undergoing surveillance, 196 had LGD at least once in the study period. Of these, 37 patients were excluded because their follow-up after the diagnosis of index dysplasia had not yet taken place. The remaining 159 patients were stratified according to the endoscopic technique used to identify the visible index lesion as follows: SDR-WLE, *n* = 80; HDR-WLE, *n* = 21; chromoendoscopic colonoscopy, *n* = 32; and invisible lesions, *n* = 26 (► Fig. 1).

Demographics

Baseline demographic and clinical parameters for the patients with visible index lesions are displayed in ► Table 1. Of all 159 patients, 97 (61.0%) were men and the majority had a diagnosis of UC (57.4%). The mean patient age at the time of detec-



tion of their index lesion was 55 years and mean disease duration was 33 years. Most index lesions in the chromoendoscopy group were found after 2010 (81.2%), while index lesions in the other groups were predominantly found before 2010.

Patients were followed for a median of 4.7 years after detection of index dysplasia. The cohort was followed for a total of 749 patient-years after index dysplasia. The duration of follow-up was significantly shorter for patients in the chromoendoscopy group (2.0 years) compared with the other groups ($P < 0.001$). In the majority of cases (74%), the visible lesions were directly removed endoscopically. Visible lesions that were not resected (26%) consisted of lesions that were deemed endoscopically unresectable (e.g. strictures), as well as lesions that should have been removed completely (e.g. polyps that were initially only biopsied).

Incidence of advanced neoplasia during follow-up

The median time to the occurrence of advanced neoplasia was 3.3 years for the whole cohort. Following detection of the index lesion, 10 patients developed an advanced neoplastic lesion (HGD, $n = 5$; CRC, $n = 5$), with an incidence rate of 1.34 cases per 100 patient-years (► **Table 2**). Kaplan–Meier curves for advanced neoplasia-free survival for all patients and for the separate groups are displayed in ► **Fig. 2**.

There were no significant differences in the incidence rates of advanced neoplasia between the groups based on endoscopic method of identification (log rank test, $P = 0.73$). The advanced lesion emerged in the same colonic segment as the in-

dex lesion in 7 of 10 patients. Five of seven visible lesions with advanced neoplasia on follow-up (71%) were reported to have been removed endoscopically, while two lesions were incompletely removed.

When the visible index lesions only were considered, the incidence rate was 0.97 per 100 patient-years. In the chromoendoscopy group, no advanced neoplasia was observed over a median period of 24 months. In the HDR-WLE group, one patient developed CRC in the same colonic segment 13 months after the index dysplasia. In this patient, the index lesion had been incompletely removed and this was later considered to have progressed to the advanced lesion.

Timelines for patients with advanced neoplasia after index dysplasia are displayed in ► **Fig. 3**.

Invisible dysplasia

In 26 patients, the index lesion was LGD in a random biopsy, without a synchronous visible dysplastic lesion. The incidence rate for advanced neoplasia in this subgroup was 2.29 per 100 patient-years ($P = 0.276$ compared with visible lesions). In five patients, LGD was detected in one or more biopsies taken from mucosa surrounding a visible dysplastic lesion. In none of these patients was advanced neoplasia found during follow-up.

A breakdown of all the different endoscopic surveillance procedures with dysplasia, including those performed after the index dysplasia had been diagnosed, is provided in ► **Table 3**.

► **Table 1** Baseline characteristics of the 133 patients with inflammatory bowel disease (IBD) who had a visible index lesion containing low grade dysplasia detected, grouped according to surveillance technique used.

	Chromoendoscopy	White-light endoscopy	P value
Number of patients	32	101	–
Male sex, n (%)	16 (50%)	65 (64.4%)	0.10
IBD diagnosis			0.75
▪ Ulcerative colitis	17 (60.4%)	54 (53.5%)	
▪ Crohn's colitis	10 (35.7%)	41 (40.6%)	
▪ Indeterminate colitis	1 (3.6%)	6 (5.9%)	
Age, mean ± SD, years	55 ± 11	56 ± 11	0.55
Age at IBD diagnosis, mean ± SD, years	30 ± 11	34 ± 13	0.21
First degree relative with colorectal cancer	3 (10.7%)	7 (6.9%)	0.34
Post-inflammatory polyps	9 (33.3%)	20 (19.8%)	0.24
Primary sclerosing cholangitis	1 (3.6%)	6 (5.9%)	0.53
Index lesion before 2010 (%)	6 (18.8%)	94 (93.1%)	<0.001
Location of index dysplasia (unifocal only)			0.29
▪ Left colon	12 (46.2%)	30 (39.5%)	
▪ Transverse colon	4 (15.4%)	14 (18.4%)	
▪ Right colon	10 (38.5%)	23 (30.3%)	
▪ Data missing	0 (0%)	9 (11.8%)	
Multifocality	6 (18.8%)	24 (23.8%)	0.66
History of dysplasia	4 (14.3%)	10 (9.9%)	0.36
Repeated finding of dysplasia	13 (40.6%)	43 (42.6%)	0.51

SD, standard deviation.

► **Table 2** Incidence of advanced neoplasia after detection of low grade dysplasia (LGD).

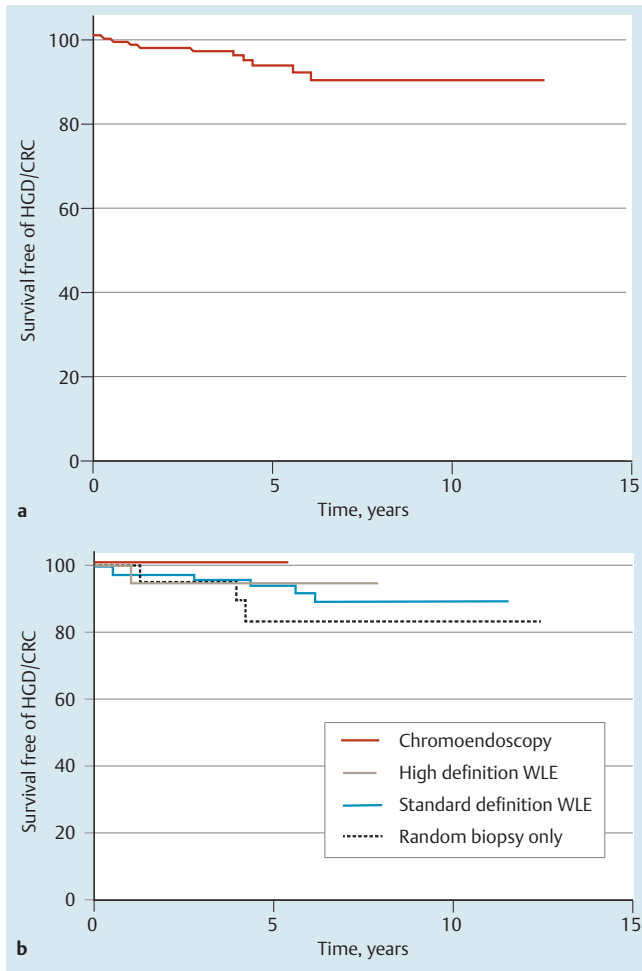
	Overall	Chromoendoscopy	HDR-WLE	SDR-WLE	Invisible
Number of patients	159	32	21	80	26
Follow-up, median (range), years	4.7 (0.2–12.6)	2.0 (0.9–5.3)	4.2 (0.2–7.8)	5.9 (0.2–11.5)	4.7 (0.5–12.6)
Advanced neoplasia, n (%) (CRC/HGD)	10 (6.3%) (5/5)	0 (0.0%)	1 (4.8%) (1/0)	6 (7.5%) (3/3)	3 (11.5%) (1/2)
Advanced neoplasia incidence rate, cases per 100 patient-years	1.34	0.0	1.24	1.29	2.29
		0.97 (all visible lesions)			
Time to advanced neoplasia, median, years	3.3	–	1.1	3.2	3.8

HDR-WLE, high definition resolution white-light endoscopy; SDR-WLE, standard definition resolution white-light endoscopy; CRC, colorectal cancer; HGD, high grade dysplasia.

The results of univariate analysis to identify additional risk factors for the occurrence of advanced neoplasia during follow-up are displayed in ► **Table 4**. None of the examined variables were found to have a significant association with the occurrence of advanced neoplasia.

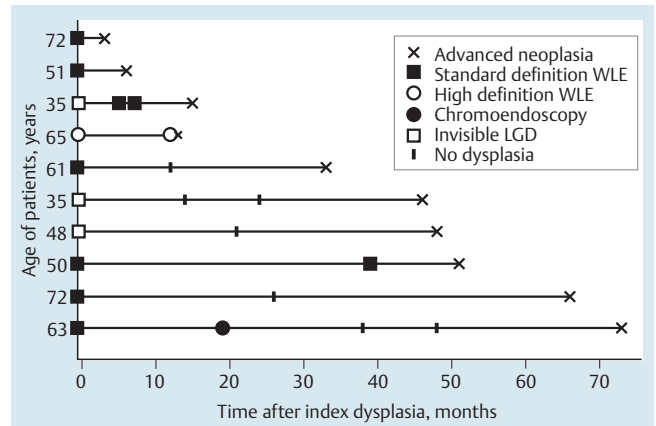
Endoscopically removed index lesions

All visible index lesions that were reported to have been removed endoscopically were analyzed separately. After excluding invisible lesions and lesions that were initially only biopsied, 89 visible index lesions remained (SDR-WLE, n=52; HDR-WLE,



► **Fig. 2** Advanced neoplasia-free survival after detection of low grade dysplasia for: **a** all 159 patients; **b** patients with lesions detected by chromoendoscopy (n = 32), high definition resolution white-light endoscopy (WLE; n = 21), standard definition resolution WLE (n = 80), and on random biopsy only (invisible lesions; n = 26). HGD, high grade dysplasia; CRC, colorectal cancer.

n = 17; chromoendoscopic colonoscopy, n = 20). Within this group, five patients developed advanced neoplasia, all of whom had an index lesion detected by SDR-WLE. No advanced neoplasia was observed after endoscopic removal of the index lesion in either the HDR-WLE or chromoendoscopy group (► **Fig. 4**).



► **Fig. 3** Timelines for patients with advanced neoplasia after index dysplasia. All invisible low grade dysplasia (LGD) was detected in random biopsies taken during standard definition resolution white-light endoscopy (SD-WLE) procedures.

Discussion

The diagnosis of LGD in the setting of IBD surveillance has been associated with a substantial risk of progression to advanced neoplasia [14, 15]. However, we found a modest overall incidence rate of 1.34 per 100 patient-years for all LGD lesions, 0.97 per 100 patient-years for visible lesions and 2.29 per 100 patient-years for invisible lesions. Furthermore, the incidence of advanced neoplasia for patients with LGD index lesions detected with either chromoendoscopy or HDR-WLE was not different.

The majority of reports on the natural history of LGD in IBD patients originate from an era in which most dysplasia was considered macroscopically invisible and endoscopically unresectable. Consequently, the occurrence of CRC during follow-up was considered to be neoplastic progression of these lesions. In a meta-analysis by Thomas et al. published in 2007 [16], pooled results of 20 studies (1982–2003) showed progression rates of 1.4 per 100 patient-years for CRC and 3.0 per 100 patient-years for a combined endpoint of dysplasia-associated lesion or mass (DALM), HGD, and CRC. Studies on the natural history of LGD published since this review have reported progression rates ranging from 4.9% to 30% (► **Table 5**). Several factors have been found to increase the risk of progression, including

► **Table 3** Comparison of endoscopic procedures in which one or more foci of visible low grade dysplasia were seen.

	Chromoendoscopy	HDR-WLE	SDR-WLE	P value
Total number of procedures	95	57	115	–
Number of visible dysplastic lesions per procedure	1.5	1.7	1.3	0.13
Number of dysplastic foci				0.11
▪ Unifocal	68 (71.6%)	33 (57.9%)	84 (73.0%)	
▪ Multifocal	27 (28.4%)	24 (42.1%)	31 (27.0%)	

HDR-WLE, high definition resolution white-light endoscopy; SDR-WLE, standard definition resolution white-light endoscopy.

► **Table 4** Univariate analysis of factors potentially associated with the incidence of advanced neoplasia on follow-up of patients with inflammatory bowel disease (IBD).

Variable	Hazard ratio (95% confidence interval)	P value
Male sex	2.35 (0.50 – 11.12)	0.28
IBD type, ulcerative colitis	1.13 (0.32 – 4.02)	0.85
Age at index lesion, years	1.00 (0.99 – 1.01)	0.88
Age at index lesion > 50 years	1.29 (0.33 – 5.01)	0.71
Age at IBD diagnosis	1.00 (0.99 – 1.01)	0.85
Age at IBD diagnosis < 30 years	0.49 (0.14 – 1.74)	0.27
Duration of IBD	1.00 (0.94 – 1.07)	0.92
Duration of IBD > 15 years	1.00 (0.26 – 3.88)	> 0.99
Post-inflammatory polyps	0.60 (0.11 – 3.23)	0.55
Primary sclerosing cholangitis	1.82 (0.23 – 14.42)	0.57
Visible lesion	0.48 (0.12 – 1.86)	0.29
Distal location of index dysplasia	1.51 (0.30 – 7.48)	0.62
Multifocal lesions	2.18 (0.56 – 8.45)	0.28
Repeated finding of dysplasia	0.30 (0.06 – 1.40)	0.12

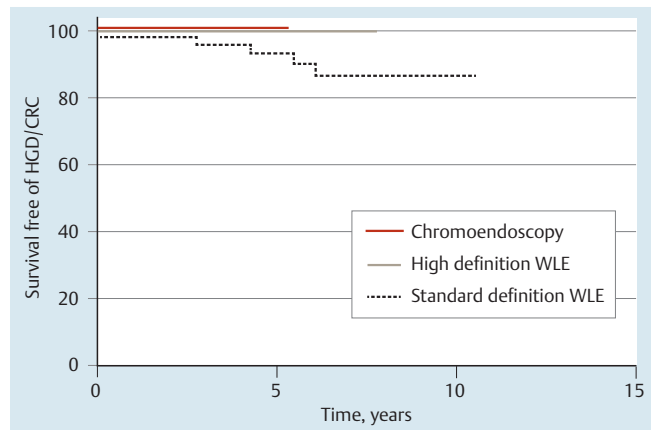
the presence of multifocal lesions [15], distal localization [17, 20], and a concurrent diagnosis of PSC [14]. Our study found lower incidence rates than previously reported and we were not able to reproduce these characteristics as independent risk factors for advanced neoplasia.

Recently, Wanders et al. performed a meta-analysis on the risk of CRC after complete resection of polypoid dysplasia, incorporating 10 studies, and calculated a pooled incidence rate of 0.7 per 100 patient-years for HGD and CRC combined [19].

► **Table 5** Overview of recent studies on the development of advanced neoplasia after detection of low grade dysplasia.

Author	Year	Study period	Patients with low grade dysplasia (visible/invisible)	Advanced neoplasia (high grade dysplasia or colorectal cancer)	Incidence rate (per 100 patient-years)
Thomas et al. (meta-analysis) [16]	2007	1982–2003	508 (31/477)	65 (12.8%)	3.0
Zisman et al. [15]	2012	1987–2002	42 (23/19)	8 (19.0%)	Not stated
Navaneethan et al. [17]	2013	1998–2011	102 (65/37)	5 (4.9%)	2.1 (distal) 0.5 (proximal)
Venkatesh et al. [14]	2013	1996–2011	10 (only PSC) (3/7)	3 (30%)	9.4
Choi et al. [18]	2015	1993–2012	172 (155/16)	33 (19.2%)	3.9
Wanders et al. (postpolypectomy meta-analysis) [19]	2014	1975–2008	376 (376/0)	12 (3.2%)	0.7

PSC, primary sclerosing cholangitis.



► **Fig. 4** Advanced neoplasia-free survival for visible lesions that were endoscopically removed (n = 89). HGD, high grade dysplasia; CRC, colorectal cancer; WLE, white-light endoscopy.

This number is far lower than reported in studies that included invisible dysplasia and is more in line with our findings. The higher incidence rate for visible lesions in our study (0.97) may be due to the fact that we included all lesions containing LGD, whereas Wanders et al. selectively looked at conventional polypoid dysplastic lesions.

In our cohort, lesions that were reported as “indefinite for dysplasia” were not selected as index lesions. However, a recent study by Lai et al. [21] reported an incidence of 1.5 cases of advanced neoplasia per 100 patient-years for patients with indefinite-for-dysplasia lesions, which is similar to the incidence rate for LGD in this study. Van Schaik et al. found a 5-year progression rate of 19% for invisible LGD and 21% for indefinite-for-dysplasia lesions, which was corrected to 37% and 5%, respectively, after review of the histologic slides [22]. Although details on the types of colonoscope used were not available in this

study, or in other reports on the follow-up of LGD, it can be assumed that SDR colonoscopes were used in this study.

Of primary interest in the current study were the patients with index lesions found using newer endoscopic techniques such as HDR-WLE and chromoendoscopy. Chromoendoscopy has repeatedly been shown to have an increased dysplasia detection rate when compared with WLE in a study setting. It should be noted however that in most trials in which chromoendoscopy was studied, a comparison was made to a group of patients undergoing SDR-WLE. Whether HDR-WLE without scheduled random biopsies will yield the same results as chromoendoscopy remains to be proven. Moreover, the clinical significance of lesions found with chromoendoscopy has not been established [23]. Some authors have hypothesized that these smaller lesions may be less advanced and therefore may have less malignant potential, yet no strong evidence in support of this hypothesis has been published to date.

In this study, we did not find a significant difference in the risk of advanced neoplasia during follow-up for index lesions detected with either WLE or chromoendoscopy, nor did we find additional risk factors regarding the index colonoscopy that were associated with the occurrence of advanced neoplasia during follow-up. On the basis of these results, the risk is similar for each LGD lesion irrespective of the endoscopic method used to detect it, although the low number of advanced neoplastic lesions may have caused a lack of power to detect more subtle differences.

A clear distinction was made between visible lesions and invisible lesions found in random biopsies, historically referred to as flat dysplasia (fLGD). Invisible dysplasia managed by endoscopic follow-up was an important subgroup in our study, as the incidence rate of advanced neoplasia was highest in these patients. This higher incidence rate may be explained by the fact that residual dysplastic mucosa was undoubtedly present in these patients. Nonetheless, it cannot be excluded that this was the result of a field cancerization effect [24]. Interestingly, however, in patients in whom biopsies from surrounding mucosa were positive for dysplasia, no advanced neoplasia occurred during follow-up.

In 23 of 26 patients, the invisible index lesions were detected before 2010. It can be argued that these lesions, previously considered invisible, would have been visible lesions in the current era following improvements in image quality, which may have rendered them amenable to resection. This trend has already been seen in clinical practice, as there has been a shift in the management of LGD from a surgical approach towards endoscopic removal [25, 26]. We excluded patients who underwent direct colectomy for LGD and it is possible that including these patients would have increased the overall risk of advanced neoplasia during follow-up in our cohort.

We found a significantly lower incidence rate of advanced neoplasia following the identification of LGD lesions as compared to previous studies [1, 27]. The observed general risk of CRC in IBD patients in the current era is lower than previously reported [5], which may reflect improved control of inflammation through the increasing use of immunomodulators or biologicals. Second, the risk of advanced neoplasia may have been

reduced owing to the fact that surveillance has reached a new level of effectiveness in detecting and removing precancerous lesions. Timely planning of follow-up procedures coupled with complete endoscopic removal of lesions will reduce most future development of CRC [28].

The strengths of the present study include the relatively large cohort, verification of the colonoscopy type used for each procedure, inclusion of patients with both UC and Crohn's colitis, and distinction between visible and invisible dysplasia. Moreover, the results are based on high quality procedures that were performed by experienced endoscopists with a special interest in IBD.

There are also some limitations to this study. First, the number of events per subgroup was relatively small, despite the large number of patients and colonoscopies included. Second, the follow-up time for the HDR-WLE and chromoendoscopy groups was limited owing to the fact that both techniques were only recently introduced. Patients in the SDR-WLE group had a longer follow-up period, with an average of 6 years. However, there are no clear indications from studies with longer follow-up times that the relative risk of advanced neoplasia is influenced by the length of the follow-up period [18, 19]. Third, because of the retrospective design of this study, it was not always possible to discern whether biopsies containing dysplastic lesions originated from previously inflamed mucosa. A proportion of the included lesions may have consisted of sporadic adenomas, which are considered to have a lower risk of neoplastic progression than colitis-associated dysplasia [3]. Fourth, it was in most cases not possible to directly link index lesions with advanced neoplasia found later on, especially because the majority of lesions were removed upon first detection. Apart from the index procedure, findings during subsequent surveillance colonoscopies are expected to further aid in determining the risk of advanced neoplasia for individual patients [29].

In summary, we observed a low rate of advanced neoplasia on follow-up after detection of LGD during IBD surveillance. This study shows no clear difference in outcomes for LGD detected by chromoendoscopy or HDR-WLE. A prospective study comparing these techniques head-to-head is needed to confirm whether the clinical significance of these lesions is indeed comparable. Our results support the notion that colectomy is no longer indicated for lesions that can be endoscopically resected.

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Competing interests

Bas Oldenburg is a consultant for AbbVie BV, Merck Sharp and Dohme BV, and Ferring BV. Evelien Dekker has equipment on loan from Olympus Europe and Fujifilm, has received a research grant from Olympus Europe, and consulted for Tillotts Pharma

(one time). The remaining authors have no conflicts of interest to disclose.

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