Gastrointestinal pathologist consensus of revised high-grade dysplasia in inflammatory bowel disease impacts the advanced neoplasia rate: a multicenter study

Maarten te Groen[a], Monica E.W. Derks[a], Iris D. Nagtegaal[b], Charlotte P. Peters[c], Annemarie C. de Vries[d], Gerard Dijkstra[e], Tessa E.H. Romkens[f], Carmen S. Horjus[g], Nanne K. de Boer[h], Michiel E. de Jong[a], Britt van Ruijven[a], Frank Hoentjen[a,i], Shoko Vos[b,*] and Lauranne A.A.P. Derikx[a,d,*] on behalf of the Dutch Initiative on Crohn's and Colitis (ICC) and the Dutch Nationwide Pathology Databank (PALGA) group

Objective The diagnosis of inflammatory bowel disease (IBD) associated with high-grade dysplasia (HGD) has a significant impact on clinical management, including colectomy. However, the prognosis of HGD remains unclear due to diagnostic uncertainty and low-quality data on subsequent synchronous and metachronous neoplasia. We aimed to evaluate a diagnostic strategy with dedicated gastrointestinal (GI) pathologist consensus of revised HGD and the impact on synchronous and metachronous neoplasia rates.

Methods In this retrospective multicenter cohort study, we used the Dutch Nationwide Pathology Databank to identify IBD patients with HGD in seven hospitals. Histopathological specimens of the initial HGD were independently revised by two dedicated GI pathologists. Definitive diagnosis was established in a consensus meeting. Synchronous and metachronous neoplasia incidences were assessed with a competing risk analysis.

Results We included 54 IBD patients with HGD, of whom 33 (61.1%) with ulcerative colitis and 42 (77.8%) with extensive disease. After consensus, 18 (33.3%) lesions were downgraded to indefinite/low-grade dysplasia, and 6 (11.1%) were revised to colorectal cancer (CRC). Seven patients (13.0%) had synchronous CRC. Patients with downgraded lesions showed a lower cumulative advanced neoplasia (HGD/CRC) incidence compared with confirmed HGD [(Gray's test $P < 0.01$), 5-year cumulative incidence 0.0% vs. 26.6%].

Conclusions We demonstrated frequent downgrading of HGD, associated with lower metachronous neoplasia rates. This underlines the potential impact of dedicated GI pathologist consensus meetings. The high and synchronous and metachronous neoplasia rates after HGD underline the need for close surveillance. Eur J Gastroenterol Hepatol 37: 287–294

European Journal of Gastroenterology & Hepatology 2025, 37:287–294

Keywords: Crohn, recurrence, treatment

[a]Department of Gastroenterology, Inflammatory Bowel Disease Centre, [b]Department of Pathology, Radboud University Medical Centre, Nijmegen, [c]Department of Gastroenterology, Amsterdam University Medical Centre, location AMC, Amsterdam, [d]Department of Gastroenterology, Erasmus Medical Centre, Rotterdam, [e]Department of Gastroenterology, Groningen University Medical Centre, Groningen, [f]Department of Gastroenterology, Jeroen Bosch Hospital, Den Bosch, [g]Department of Gastroenterology, Rijnstate Hospital, Arnhem, [h]Department of Gastroenterology and Hepatology, AGEM Research Institute, Amsterdam University Medical Centre, location Vrije Universiteit Amsterdam, Amsterdam, the Netherlands and [i]Division of Gastroenterology, Department of Medicine, University of Alberta, Edmonton, Canada

Correspondence to Maarten te Groen, MD, PhD, Department of Gastroenterology, Inflammatory Bowel Disease Centre, Radboud University Medical Centre, Nijmegen 6525GA, the Netherlands
Tel: +31 6 43232906; e-mail: maarten.tegroen@radboudumc.nl

*Shoko Vos and Lauranne A.A.P. Derikx shared last authorship.

Received 15 August 2024 **Accepted** 7 October 2024.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.eurojgh.com.

Introduction

Inflammatory bowel disease (IBD) patients bear an increased colorectal cancer (CRC) risk and undergo regular endoscopic surveillance to detect and remove premalignant lesions. CRC may develop via an inflammation-dysplasia-carcinoma pathway, with high-grade dysplasia (HGD) as the highest risk precursor. Following a diagnosis of colonic HGD, endoscopic resection is recommended while surgical resection is recommended for endoscopically irresectable lesions [1–3].

The finding of HGD comes with a high risk of synchronous CRC and metachronous advanced neoplasia (AN) (HGD and/or CRC). Synchronous (0–45.5%) and metachronous (0–67%) rates after a diagnosis of HGD vary widely [4–8]. Methodological limitations, especially in older studies, contribute to this wide range and include (1) lack of a standardized surveillance strategy, (2) use of fiber-optic endoscopy with a higher risk of missing smaller, IBD-related lesions compared with high-definition video-endoscopy, and (3) missing or limited follow-up after HGD. Up-to-date information is needed to provide accurate synchronous and metachronous

neoplasia rates. However, the most important caveat is the uncertainty of a 'true' HGD diagnosis, since the histopathological interobserver agreement for HGD in IBD is moderate at best [9–11]. HGD could be considered the tipping point between endoscopic and surgical treatment in the inflammation-dysplasia-CRC sequence. Consequently, inaccurate HGD diagnoses might result in over- or undertreatment.

Differentiation between grades of neoplasia can be hampered by the quality of biopsy sampling and the presence of severe inflammation [12,13]. Current guidelines suggest consultation of a second gastrointestinal (GI) pathologist to assess a diagnosis of HGD, although there are no IBD studies to support (the impact of) this recommendation [1,3,14]. In line, data on the optimal approach in case of disagreement between pathologists is lacking. Pathologist consensus meetings have shown to improve diagnostic accuracy of low-grade dysplasia (LGD) in IBD resulting in improved targeted treatment and accuracy of prognosis [15,16]. It is unknown whether these observations also apply to HGD in IBD.

In this study, we aimed to assess the impact of a diagnostic strategy with dedicated GI pathologist consensus meetings for revised HGD on the synchronous and metachronous neoplasia incidence.

Methods

Study design

A retrospective multicenter cohort study was performed to determine the outcomes of HGD before and after histopathological revision and dedicated GI pathologist consensus.

Patients

A search was performed in the Dutch Nationwide Pathology Databank (PALGA, search lzv2019-87) to identify IBD patients with HGD in five academic and two large community hospitals (IBD-population >1900 patients). All centers adhere to the Dutch surveillance guideline, which closely resembles the British Society of Gastroenterology guideline [1,17]. The PALGA registry has nationwide coverage since 1991, with good accuracy for IBD [18]. All reports have a unique identifier that links pathology reports to individual electronic patient records. We combined search terms for IBD ('ulcerative colitis', 'Crohn's disease', 'indeterminate colitis', and 'chronic idiopathic inflammatory bowel disease') and neoplasia ('high-grade dysplasia', 'carcinoma in situ', and 'colorectal cancer) with localization in the colon or rectum to identify IBD patients with HGD. Reports up to 1 December 2020 were collected.

Patients were included if they met the following criteria: (1) an established diagnosis of ulcerative colitis (UC), colonic Crohn's disease (CD), or IBD-unclassified, and (2) a histological diagnosis of HGD. Patients were excluded in case of (1) AN before IBD diagnosis, or (2) a familial CRC syndrome, or (3) no available histological specimens, or (4) CRC simultaneously detected as HGD, since management decisions are based on the highest neoplasia grade.

Outcomes

Primary outcomes were (1) changes in histopathological diagnosis after a dedicated GI pathologist consensus meeting, (2) the synchronous CRC incidence, and (3) the cumulative incidence of metachronous neoplasia, considering (a) all types of neoplasia and (b) AN.

Synchronous CRC was defined as histologically confirmed CRC during the subsequent therapeutic procedure for initial HGD. Thus, these CRCs were not recognized during the initial diagnostic HGD procedure, although it is very likely they were already present. Patients with simultaneously diagnosed HGD and CRC were excluded from this study and are, therefore, not contributing to synchronous CRC rates. Metachronous neoplastic lesions were defined as histologically confirmed indefinite for dysplasia (IND), LGD or AN during follow-up after treatment of HGD.

Revision and dedicated gastrointestinal pathologist consensus

All available HGD histology specimens from the initial procedure at which HGD was detected were retrieved from the participating centers. Histopathological and clinical information was blinded before revision was performed, except for initial dysplasia grade (which was HGD in all cases). Revision was defined as the process in which each specimen was individually reviewed for a final diagnosis in random order by two dedicated GI pathologists (S.V. and I.N.) from an academic teaching hospital (Radboud University Medical Center, Nijmegen, The Netherlands) with experience in the field of IBD. All specimens were stained with hematoxylin and eosin and reviewed physically (glass slides) or digitally depending on availability. If multiple slides from one lesion were present, all slides were assessed. All specimens were graded using the classification by Riddell *et al*. [12] as absence of dysplasia, IND, LGD, HGD, or CRC. According to this classification, HGD shows nuclear stratification extending into the luminal part of the epithelial cells as opposed to LGD, and may include extensive hyperchromatism, pleomorphism, and loss of nuclear polarization as well. In case neoplastic changes extend beyond the muscularis mucosae, lesions are considered CRC. Only the most advanced grade observed in a specimen was recorded. Only in case of disagreement between individual pathologists, specimens were discussed in a separate consensus meeting (attendees: S.V. and I.N.) to reach a definitive diagnosis.

Data collection

Extracted variables consisted of IBD duration and subtype, familial CRC, smoking, IBD extent (Montreal classification [19] or in case of CD, <50% or >50% inflamed colon), prior colonic surgery, primary sclerosing cholangitis (PSC). Extensive disease was defined as >50% histologically inflamed colon for CD or Montreal E3 for UC. All neoplasia data per case were extracted, including date of diagnosis, type of procedure, grade, location, shape (polypoid visible, nonpolypoid visible or invisible, the latter detected with random biopsies [20]), and endoscopic

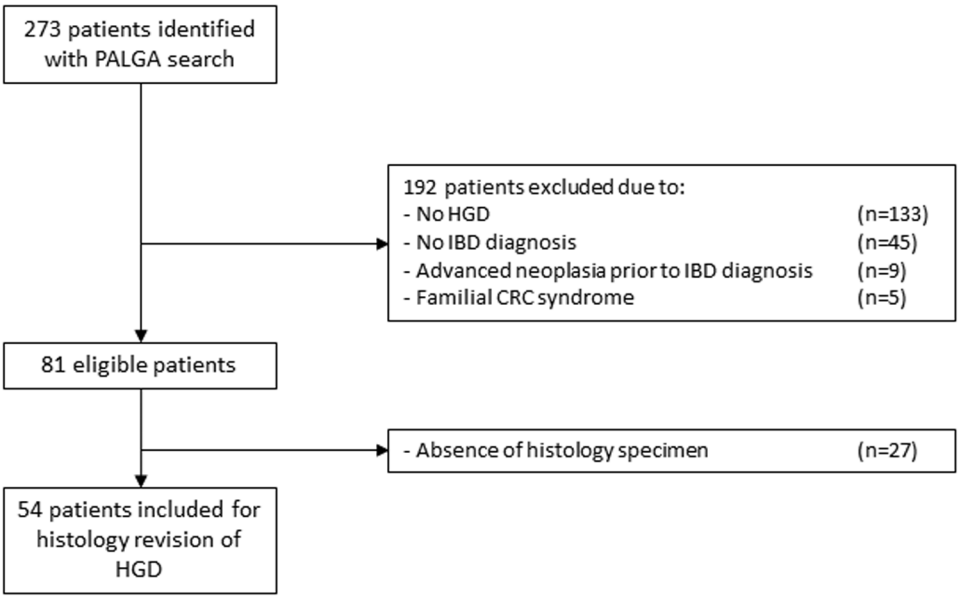

Fig. 1. Patient selection flowchart. CRC, colorectal cancer; HGD, high-grade dysplasia; IBD, inflammatory bowel disease.

or surgical retrieval. Collected treatment data included modality and incomplete resections (microscopically or macroscopically visible residue).

Statistics

We reported continuous outcomes as medians with interquartile range (IQR) and categorical outcomes as frequencies with percentages. Differences were assessed with chi-square or Fischer's exact tests or the Kruskall–Wallis test. Interobserver agreement for HGD revision was determined with Cohen's Kappa (K). Coefficients ≤0.20, 0.21–0.40, 0.41–0.60, 0.61–0.80, and >0.80 were classified as poor, fair, moderate, good, and very good agreement, respectively [21]. Neoplasia dates were categorized into 5-yearly periods (<2005, 2005–2010, 2011–2015, and >2015) to assess differences in revised diagnoses over time. Time until metachronous neoplasia was assessed for patients without synchronous CRC with cumulative incidence functions and Gray's tests, using proctocolectomy and death as competing event since these may preclude metachronous lesions [22,23]. Hence, patients with proctocolectomy as initial HGD treatment were not assessed for this analysis. Follow-up duration was defined as the time between HGD treatment and the event of interest (metachronous neoplasia or metachronous AN depending on the analysis), competing event or last endoscopic procedure, whichever occurred first. Incidence rates and cumulative incidences were displayed with 95% confidence intervals (CIs). A two-sided *P*-value <0.05 was considered statistically significant.

A sensitivity analysis was performed to assess potential inclusion bias, comparing patients with and without available histology specimens from the PALGA search. All analyses were performed with SPSS v25 (Armonk, New York, USA) and R (v3.5.3, packages '*survminer*', '*cmprsk*').

Ethical considerations

This study was approved by the scientific committee of PALGA (lzv2019-87) and the institutional review board of the Radboud University Medical Centre (2017-3219).

Results

Baseline characteristics

The PALGA search resulted in 54 IBD patients with HGD after applying exclusion criteria (Fig. 1). Of these, 34 (63.0%) were male and 33 (61.1%) had UC (Table 1). Median IBD duration until HGD was 18.5 (IQR: 11.0–28.8) years. HGD was diagnosed during a colonoscopy ($n = 44$, 81.5%) or colectomy ($n = 10$, 18.5%, indicated for recurrent/multifocal LGD ($n = 6$) or therapy refractory disease ($n = 4$)]. Colonic HGD location and morphology are shown in Fig. 2.

Forty-eight (88.9%) HGD lesions were diagnosed in (historically) inflamed colonic mucosa. Nineteen patients had a prior diagnosis of LGD (35.2%), IND ($n = 2$, 3.7%) or both ($n = 2$, 3.7%). Seven (13.0%) patients underwent a surgical resection before HGD diagnosis [partial colectomy $n = 5$ (9.2%), (sub)total colectomy $n = 2$ (3.7%)].

Dedicated gastrointestinal pathologist consensus

The two pathologists agreed with the original diagnosis of HGD in 36 (66.7%) and 17 (31.5%) patients, respectively (Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/EJGH/B100*). Interobserver disagreement between the two pathologists was reported in 18 (32.7%) patients between HGD and LGD, in three (5.6%) between HGD and CRC and in one (1.8%) between IND and absence of dysplasia. This resulted in a fair interobserver agreement (K: 0.31, 95% CI: 0.12–0.49) between the two dedicated GI pathologists. After the histologic revision and consensus meeting with the two dedicated GI pathologists,

Table 1. Cohort characteristics

Characteristics	Before revision and consensus	After revision and consensus			
	HGD (*n* = 54)	IND/LGD (*n* = 18)	HGD (*n* = 30)	CRC (*n* = 6)	*P* value
Male sex, *n* (%)	34 (63.0)	12 (66.7)	18 (60.0)	4 (66.7)	0.88
Disease type, *n* (%)					
Ulcerative colitis	33 (61.1)	12 (66.7)	19 (63.3)	2 (33.3)	0.51
Crohn's disease	19 (35.2)	5 (27.8)	10 (33.3)	4 (66.7)	
IBD-undetermined	2 (3.7)	1 (5.6)	1 (3.3)	0 (0.0)	
Age at IBD diagnosis in years, median (IQR)	31.5 (19.0–45.0)	41.0 (22.0–46.8)	28.0 (20.5–43.3)	20.5 (19.0–40.0)	0.32
Time until lesion in years, median (IQR)	18.5 (11.0–28.8)	16.0 (10.8–25.0)	18.5 (11.0–31.3)	27.0 (18.5–37.0)	0.23
Lesion morphology[a], *n* (%)					
Polypoid	26 (49.1)	15 (83.3)	10 (34.5)	1 (16.7)	<0.01
Nonpolypoid	20 (37.7)	3 (16.7)	13 (44.8)	4 (66.7)	
Invisible	7 (13.7)	0 (0.0)	6 (20.7)	1 (16.7)	
Multifocal lesion, *n* (%)	19 (35.2)	6 (33.3)	11 (36.7)	2 (33.3)	0.97
Maximal endoscopic disease extent (Montreal), *n* (%)					
E1	3 (5.6)	2 (11.1)	1 (3.3)	0 (0.0)	0.56
E2	4 (7.4)	1 (5.6)	3 (10.0)	0 (0.0)	
E3	30 (55.6)	11 (61.1)	17 (56.7)	2 (33.3)	
<50% (Crohn's disease)	5 (9.3)	2 (11.1)	(6.7)	1 (16.7)	
>50% (Crohn's disease)	12 (22.2)	2 (11.1)	7 (22.3)	3 (50.0)	
Maximal histological disease extent (Montreal), *n* (%)					
E1	9 (16.7)	5 (27.8)	4 (13.3)	0 (0.0)	0.46
E2	4 (7.4)	1 (5.6)	3 (10.0)	0 (0.0)	
E3	6 (48.1)	9 (50.0)	15 (50.0)	2 (33.3)	
<50% (Crohn's disease)	4 (7.4)	1 (5.6)	2 (6.7)	1 (16.7)	
>50% (Crohn's disease)	11 (20.4)	2 (11.1)	6 (20.0)	3 (50.0)	
For Crohn's disease: disease behavior (Montreal), *n* (%)					
B1	4 (21.1)	1 (20.0)	2 (20.0)	1 (25.0)	0.72
B2	6 (31.6)	2 (40.0)	3 (30.0)	1 (25.0)	
B3	4 (21.1)	2 (40.0)	1 (10.0)	1 (25.0)	
B2 + 3	5 (26.3)	0 (0.0)	4 (40.0)	1 (25.0)	
P	7 (13.0)	2 (11.1)	4 (13.3)	1 (16.7)	
Medication exposure, *n* (%)					
5-aminosalicylates	30 (58.8)	14 (82.4)	12 (42.9)	4 (66.7)	0.59
Immunomodulators	19 (35.2)	6 (33.3)	10 (33.3)	3 (50.0)	
Biologicals/small molecules/ciclosporin	16 (31.4)	5 (29.4)	10 (35.7)	1 (16.7)	
BSG guideline colorectal cancer risk stratification [1], *n* (%)					
No indication	8 (14.8)	2 (11.1)	6 (20.0)	0 (0.0)	0.77
Low	5 (9.3)	2 (11.1)	2 (6.7)	1 (16.7)	
Intermediate	17 (31.5)	5 (27.8)	9 (30.0)	3 (50.0)	
High	24 (44.4)	9 (50.0)	13 (43.3)	2 (33.3)	
For ulcerative colitis/IBD-undetermined: stricture, *n* (%)	6 (11.1)	1 (7.7)	5 (28.3)	0 (0.0)	0.38
Family history of colorectal cancer, *n* (%)	7 (13.0)	3 (16.7)	3 (10.0)	1 (16.7)	0.80
Smoking[b], *n* (%)					
Current	3 (5.6)	0 (0.0)	2 (6.7)	1 (16.7)	0.69
Past	11 (20.4)	3 (16.7)	7 (23.3)	1 (16.7)	
Never	34 (63.0)	13 (72.2)	17 (56.7)	4 (66.7)	
Primary sclerosing cholangitis, *n* (%)	12 (22.2)	6 (33.3)	6 (20.0)	0 (0.0)	0.21
Postinflammatory polyps, *n* (%)	19 (35.2)	7 (38.9)	10 (33.3)	2 (33.3)	0.92
Prior dysplasia (IND/LGD), *n* (%)	23 (42.6)	8 (44.4)	12 (40.0)	3 (50.0)	0.89
Academic center, *n* (%)	47 (87.0)	15 (83.3)	27 (90.0)	5 (87.0)	0.77

BSG, British Society of Gastroenterology; CRC, colorectal cancer; HGD, high-grade dysplasia; IND, indefinite for dysplasia; IQR, interquartile range; LGD, low-grade dysplasia.
[a]Two missings.
[b]Six missings.

17 (31.5%) lesions were downgraded to LGD, one (1.9%) to IND and six (11.1%) were upgraded to CRC (Table 1). Nine (16.7%) and 13 (24.0%) revised diagnoses made by the individual dedicated GI pathologists were changed after consensus, respectively. None of the upgraded lesions to CRC were considered IND or LGD by one of the individual pathologists before the consensus meeting.

The total number of changed diagnoses after revision and dedicated GI pathologist consensus did not differ over time ($P = 0.38$, Supplementary Table 2, Supplemental digital content 1, *http://links.lww.com/EJGH/B100*). Examples of LGD, HGD, and CRC after revision and dedicated GI pathologist consensus are displayed in Supplementary Fig. 1, Supplemental digital content 1, *http://links.lww.com/EJGH/B100*.

Treatment

HGD, as established before revision and dedicated GI pathologist consensus, was treated endoscopically in 22 (40.7%) patients and surgically in 31 patients (57.4%, Table 2). Median time from HGD diagnosis until treatment was 4 weeks (IQR: 0.0–11.5 weeks). One patient with HGD and PSC passed away due to cholangitis before the HGD lesion could be treated.

In retrospect, downgraded lesions following revision and dedicated GI pathologist consensus were not more frequently treated with endoscopic resection than confirmed HGD or CRC [IND/LGD: $n = 10$ (55.6%) vs. HGD: $n = 10$ (33.3%) vs. CRC: $n = 2$ (33.3%), $P = 0.29$, Table 2].

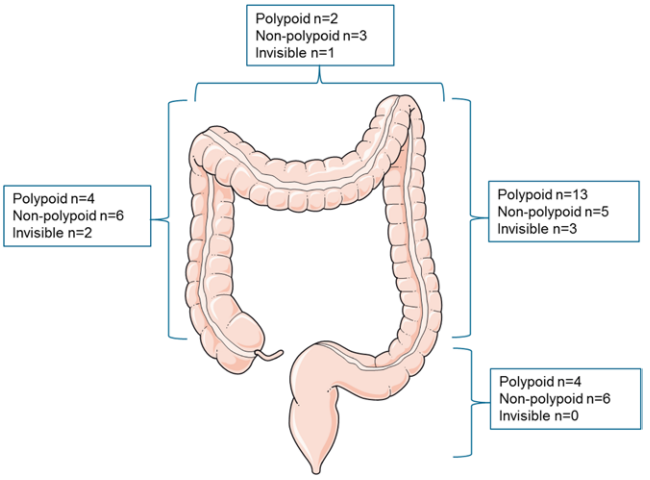

Fig. 2. HGD Localization and morphology* [24]. **n* = 5 patients with multifocal lesions in different colonic segments not included.

Table 2. Treatment characteristics

	Before revision and consensus	After revision and consensus		
	HGD (*n* = 54)	IND/LGD (*n* = 18)	HGD (*n* = 30)	CRC (*n* = 6)
Treatment type, *n* (%)				
Endoscopic resection	22 (40.7)	10 (55.6)	10 (34.5)	2 (33.3)
Partial colectomy	10 (18.5)	2 (11.1)	5 (17.2)	3 (50.0)
(Sub)total colectomy	9 (16.7)	2 (11.1)	7 (24.1)	0 (0.0)
Proctocolectomy	12 (22.2)	4 (22.2)	7 (24.1)	1 (16.7)
No treatment	1 (1.9)	0 (0.0)	1 (3.3)	0 (0.0)
Incomplete resection[a], *n* (%)	3 (5.6)	1 (5.6)	1 (3.3)	1 (16.7)

CRC, colorectal cancer; HGD, high-grade dysplasia; IND, indefinite for dysplasia; LGD, low-grade dysplasia.
[a]13 missings.

Synchronous colorectal cancer

Seven patients (13.0%) with endoscopically diagnosed HGD had synchronous CRC in the surgical resection specimen, not detected during the initial HGD diagnostic procedure. Synchronous CRC was associated with initial nonpolypoid HGD (*n* = 6 (85.7%) vs. *n* = 14 (30.4%), *P* = 0.01, Supplementary Table 3, Supplemental digital content 1, *http://links.lww.com/EJGH/B100*). Two synchronous CRCs (28.6%) were present in patients with a revised diagnosis of CRC following dedicated GI pathologist consensus, whereas five (71.4%) had confirmed HGD after revision. No synchronous CRC was observed in patients with a downgraded lesion [*n* = 0 (0.0%) in IND/LGD vs. *n* = 7 (19.4%) in AN, *P* = 0.04]. Synchronous CRC was diagnosed median 8 weeks (IQR: 4.0–13.0) after initial HGD diagnosis.

Metachronous neoplasia

The median endoscopic follow-up after treatment was 28 months (IQR: 10.0–74.0 months), in which median 2 (IQR: 1–4) endoscopies were performed. Median follow-up for patients with confirmed IND/LGD, HGD, or CRC was 69 months (IQR: 8.0–106.5), 23 months (IQR: 7.0–45.0), and 14 months (IQR: 9.0–14.0), respectively.

Outcomes of 46 (85.2%) treated patients without synchronous CRC (*n* = 7) were assessed. Before revision and dedicated GI pathologist consensus, 16 (34.8%) patients were diagnosed with metachronous neoplasia (IND/LGD: *n* = 7, HGD: *n* = 8; CRC: *n* = 1) after a median follow-up of 14 months (IQR: 4.0–42.8). Median time until metachronous AN was 23 months (IQR: 8.5–85.5 months, Fig. 3 and Supplementary Fig. 2A and B, Supplemental digital content 1, *http://links.lww.com/EJGH/B100*). There was no significant difference in the cumulative metachronous AN incidence between unifocal or multifocal index HGD (19.3 vs. 16.7%, respectively, Gray's test *P* = 0.98). The only patient who developed metachronous CRC after 131 months was diagnosed with recurrent LGD during follow-up but refused a colectomy (Fig. 3).

Patients with a downgraded lesion showed a lower cumulative incidence of metachronous AN compared with those with confirmed HGD or upgrade to CRC [(Gray's test *P* < 0.01), 5-year cumulative incidence 0.0% (IND/LGD) vs. 26.6% (HGD), Fig. 4a]. Of note, the two patients with a retroactive upgrade from HGD to CRC who were treated with endoscopic resection were both diagnosed with metachronous AN during follow-up. The cumulative incidence of metachronous neoplasia (including IND/LGD and AN during follow-up) was not significantly different between downgraded lesions and confirmed AN (Gray's test *P* = 0.30, Fig. 4b). Cumulative incidence functions including competing event curves are displayed in Supplementary Fig. 3A and B, Supplemental digital content 1, *http://links.lww.com/EJGH/B100*.

Sensitivity analysis

The cumulative incidence of metachronous AN did not differ between patients without histopathological HGD specimen available [and therefore excluded from main analyses (*n* = 27, Fig. 1) and those with specimens available (*n* = 54, *P* = 0.42).

Discussion

In this multicenter study including 54 IBD patients with colonic HGD, we observed a significant impact of dedicated GI pathologist consensus on revised HGD diagnoses, which resulted in a downgraded diagnosis to IND or LGD in more than one-third of the patients, with only half of the diagnoses confirmed as HGD. Patients with downgraded lesions showed a lower cumulative incidence of metachronous AN after treatment, whereas patients with confirmed HGD demonstrated a higher cumulative incidence (5-year cumulative incidence 0.0 vs. 26.6%).

We observed frequent down- and upgrading of revised HGD after GI pathologist consensus. To our knowledge, only one other study on IBD-related neoplasia assessed the effectiveness of dedicated GI pathologist consensus by means of an expert panel, only including patients with LGD [15]. The authors demonstrated that pathologist consensus significantly improved the prognostic value for AN development. Similarly, in Barrett's esophagus, pathologist expert panel assessment resulted in improved risk stratification and improved neoplasia-free survival [16,25]. We suggest that a dedicated GI pathologist consensus meeting could be an effective intervention for cases

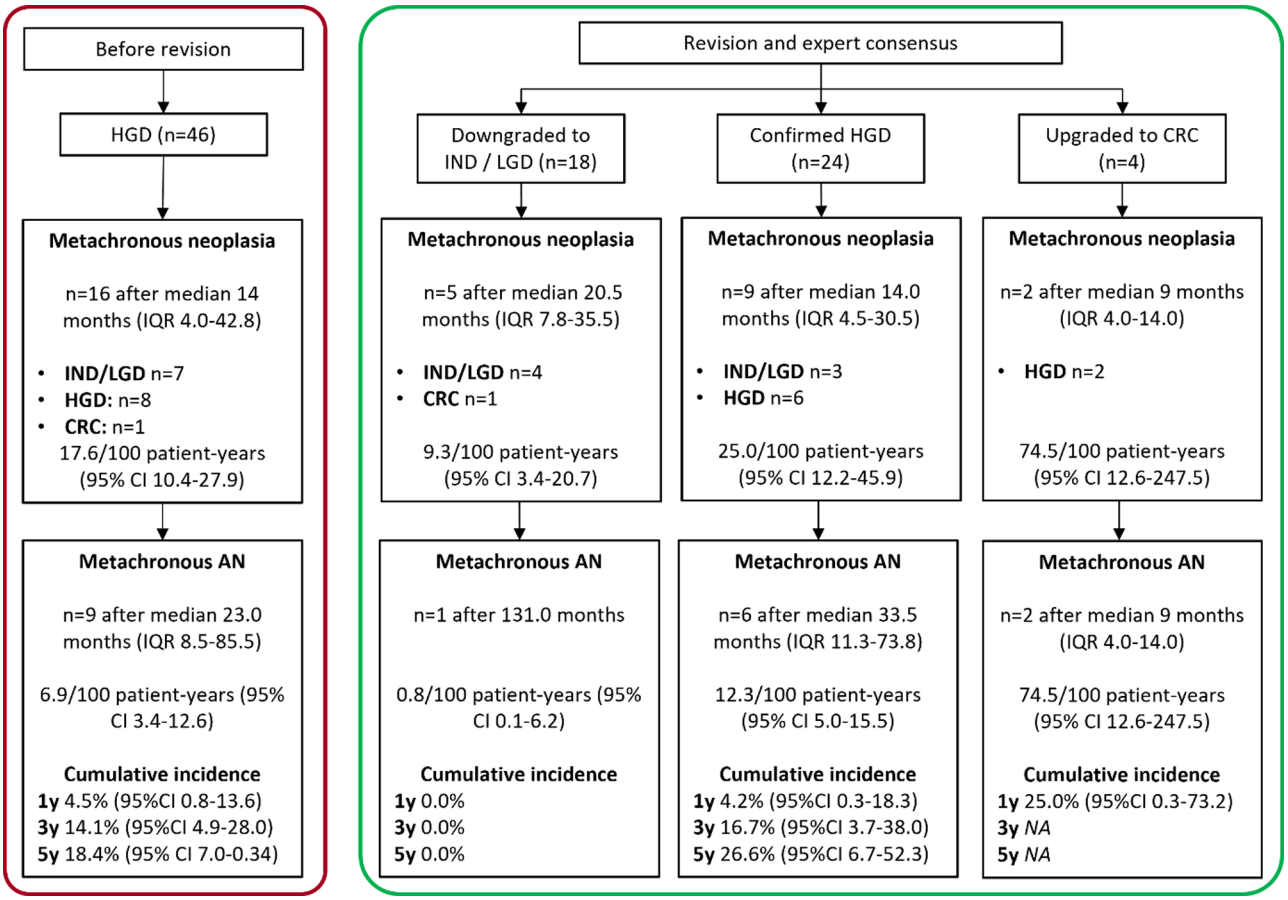

Fig. 3. Overview of (cumulative) metachronous neoplasia incidence after revision with dedicated GI pathologist consensus, excluding synchronous CRC (*n* = 7). AN, advanced neoplasia; CI, confidence interval; CRC, colorectal cancer; HGD, high-grade dysplasia; IND, indefinite for dysplasia; IQR, interquartile range; LGD, low-grade dysplasia; NA, not available; PY, patient-years; y, year.

with disagreement between pathologists, underlined by the significantly lower cumulative incidence of metachronous AN in patients with revised IND/LGD in this study.

The clinical consequences of HGD are significant, with a 5-year cumulative incidence of metachronous AN of 26.6%. HGD can be considered a tipping point between endoscopic treatment and colectomy. An accurate diagnosis is, therefore, essential for the prevention of both under- and overtreatment. In our cohort, eight (44.4%) patients with a diagnosis of IND/LGD after dedicated GI pathologist consensus underwent a colectomy based on the initial diagnosis of HGD. By contrast, two (33.3%) patients with an upgrade to CRC after consensus initially underwent an endoscopic resection, thus in retrospect deviating from the guidelines' recommendations.

Importantly, even after accurate diagnosis of HGD, the metachronous AN and synchronous CRC rates are high. Compared with LGD, HGD harbors an almost three times higher 5-year cumulative incidence of metachronous AN (26.6% vs. 8.5%) [18]. This emphasizes the need for strict surveillance, especially in case of remaining colon after treatment. Synchronous CRC rates of 28.9 and 45.5% after an initial HGD diagnosis were reported in the two largest cohort studies so far, using historical data from 1984 to 2013 [7,26]. We observed a lower, but substantial rate of 13.0%. This is in line with a recent meta-analysis, showing a pooled estimated synchronous CRC rate of 13.7% [8]. Clinicians should be aware of this high synchronous CRC rate whilst deciding on HGD management.

Strengths of this study include the use of a nationwide pathology databank combined with clinical data from seven large academic and nonacademic hospitals. This enabled us, despite its relatively rare occurrence, to compile this HGD cohort representative of the IBD population at large. It has resulted in the largest longitudinal database of HGD in IBD to date. Furthermore, we performed competing risk analyses, preventing overestimation of metachronous neoplasia rates [27].

There are also limitations, including the retrospective study design. As a consequence, histopathological HGD specimens were not available for all HGD patients. However, our sensitivity analysis did not indicate selection bias. IBD-associated neoplasia is typically nonpolypoid (flat or invisible) with higher recurrence rates compared with sporadic neoplasia. Only 50% of lesions in our study were morphologically polypoid, which may have impacted metachronous neoplasia rates. Nevertheless, 90% of all lesions were located in (previously) inflamed colonic mucosa. Furthermore, synchronous lesions could not be differentiated from the result of sampling error or initially missed multifocal lesions. Specimens from biopsied lesions might have not been representative of the true neoplasia grade of the entire lesion, potentially

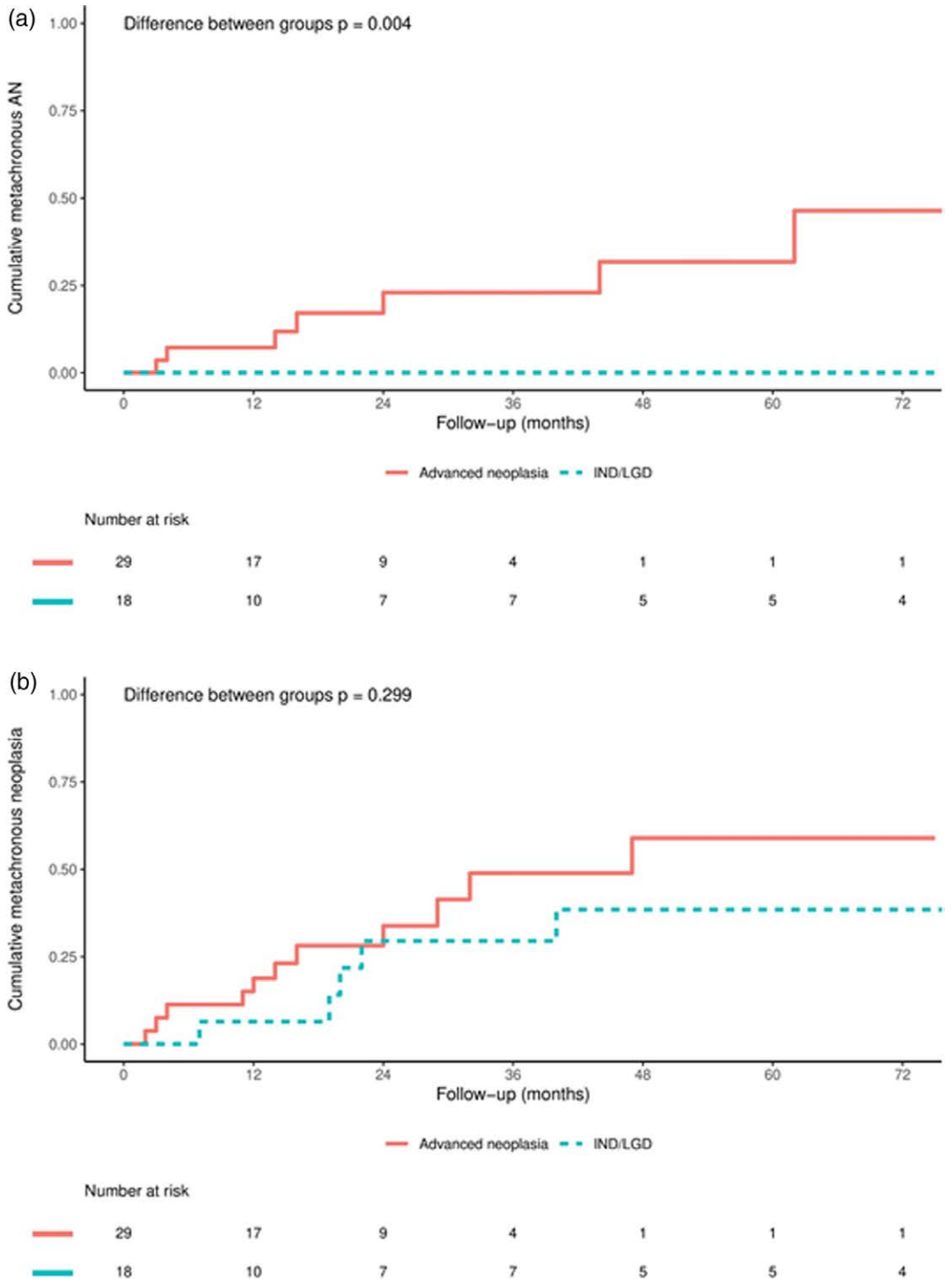

Fig. 4. (a and b) Cumulative incidence function for (a, upper) metachronous advanced neoplasia (b, lower) and metachronous neoplasia (any type: IND/LGD or advanced neoplasia), after revision and dedicated GI pathologist consensus. AN, advanced neoplasia; GI, gastrointestinal; IND, indefinite for dysplasia; LGD, low-grade dysplasia.

impacting synchronous and metachronous neoplasia rates. The metachronous neoplasia incidences found in this study are influenced by the contemporary selection of HGD treatment modality, although these are representative of clinical practice. Furthermore, the relatively long inclusion period may impact our findings given the altered and improved endoscopic surveillance strategies and techniques over time.

Our concept of individual pathologist revision followed by a plenary consensus meeting for specimen with disagreement can be considered as a practical implementation of a dedicated GI panel, similar to other studies on the accuracy of diagnostics [28]. Centralized and combined expertise of dedicated GI pathologists, gastroenterologists, and surgeons could offer improved patient care for IBD patients with HGD as well as lower treatment costs [16,29,30].

In conclusion, this multicenter study showed that after dedicated GI pathologist consensus, more than one-third of revised HGD lesions were downgraded, corresponding with a lower cumulative incidence of metachronous AN. In retrospect, this may have resulted in overtreatment by colectomy for this group. Synchronous and metachronous AN frequently occurred, underlining the importance of strict surveillance adherence following a confirmed diagnosis of HGD.

Acknowledgements

The authors thank N. den Broeder, MSc, for statistical input and advice.

Conceptualization, methodology, formal analysis, data acquisition, writing (both draft and final version), project administration, and approval of final version: M.G. and M.E.W.D. Conceptualization, data acquisition, writing (both draft and final version), reviewing, and approval of final version: I.D.N., S.V., F.H., and L.A.A.P.D. Data acquisition, reviewing, and approval of final version: C.P.P., A.C.V., G.D., T.E.H.R., C.S.H., N.K.B., M.E.J., and B.R.

This work was presented as oral presentation at the Dutch Digestive Disease Days 2022, the Netherlands (digital), and as poster presentation at the Digestive Disease Week 2022, San Diego, California, USA.

Conflicts of interest

There are no conflicts of interest.

References

1 Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, *et al*; IBD guidelines eDelphi consensus group. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019; 68:s1–s106.
2 Magro F, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, *et al*; European Crohn's and Colitis Organisation [ECCO]. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. *J Crohns Colitis* 2017; 11:649–670.
3 Murthy SK, Feuerstein JD, Nguyen GC, Velayos FS. AGA clinical practice update on endoscopic surveillance and management of colorectal dysplasia in inflammatory bowel diseases: expert review. *Gastroenterology* 2021; 161:1043–1051.e4.
4 Bernstein CN, Shanahan F, Weinstein WM. Are we telling patients the truth about surveillance colonoscopy in ulcerative colitis? *Lancet* 1994; 343:71–74.
5 Blonski W, Kundu R, Furth EF, Lewis J, Aberra F, Lichtenstein GR. High-grade dysplastic adenoma-like mass lesions are not an indication for colectomy in patients with ulcerative colitis. *Scand J Gastroenterol* 2008; 43:817–820.
6 Korelitz BI, Sultan K, Kothari M, Arapos L, Schneider J, Panagopoulos G. Histological healing favors lower risk of colon carcinoma in extensive ulcerative colitis. *World J Gastroenterol* 2014; 20:4980–4986.
7 Choi CH, Ignjatovic-Wilson A, Askari A, Lee GH, Warusavitarne J, Moorghen M, *et al*. Low-grade dysplasia in ulcerative colitis: risk factors for developing high-grade dysplasia or colorectal cancer. *Am J Gastroenterol* 2015; 110:1461–71; quiz 1472.
8 Kabir M, Fofaria R, Arebi N, Bassett P, Tozer PJ, Hart AL, *et al*. Systematic review with meta-analysis: IBD-associated colonic dysplasia prognosis in the videoendoscopic era (1990 to present). *Aliment Pharmacol Ther* 2020; 52:5–19.
9 Odze RD, Goldblum J, Noffsinger A, Alsaigh N, Rybicki LA, Fogt F. Interobserver variability in the diagnosis of ulcerative colitis-associated dysplasia by telepathology. *Mod Pathol* 2002; 15:379–386.
10 Eaden J, Abrams K, McKay H, Denley H, Mayberry J. Inter-observer variation between general and specialist gastrointestinal pathologists when grading dysplasia in ulcerative colitis. *J Pathol* 2001; 194:152–157.
11 Leoncini G, Donato F, Reggiani-Bonetti L, Salviato T, Cadei M, Daperno M, *et al*; IG-IBD Pathology Group. Diagnostic interobserver variability in Crohn's disease- and ulcerative colitis-associated dysplasia: a multicenter digital survey from the IG-IBD Pathologists Group. *Tech Coloproctol* 2021; 25:101–108.
12 Riddell RH, Goldman H, Ransohoff DF, Appelman HD, Fenoglio CM, Haggitt RC, *et al*. Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. *Hum Pathol* 1983; 14:931–968.
13 Kawachi H. Histopathological diagnosis of ulcerative colitis-associated neoplasia. *Dig Endosc* 2019; 31:31–35.
14 Laine L, Kaltenbach T, Barkun A, McQuaid KR, Subramanian V, Soetikno R; SCENIC Guideline Development Panel. Scenic international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. *Gastroenterology* 2015; 148:639–651.e28.
15 van Schaik FD, ten Kate FJ, Offerhaus GJ, Schipper ME, Vleggaar FP, van der Woude CJ, *et al*; Dutch Initiative on Crohn and Colitis. Misclassification of dysplasia in patients with inflammatory bowel disease: consequences for progression rates to advanced neoplasia. *Inflamm Bowel Dis* 2011; 17:1108–1116.
16 Duits LC, Phoa KN, Curvers WL, Ten Kate FJ, Meijer GA, Seldenrijk CA, *et al*. Barrett's oesophagus patients with low-grade dysplasia can be accurately risk-stratified after histological review by an expert pathology panel. *Gut* 2015; 64:700–706.
17 van Bodegraven AA, van Everdingen JJE, Dijkstra G, de Jong DJ, Oldenburg B, Hommes DW; CBO-werkgroep 'IBD bij volwassenen'. [Guideline 'Diagnosis and treatment of inflammatory bowel disease in adults'. I. Diagnosis and treatment]. *Ned Tijdschr Geneeskd* 2010; 154:A1899.
18 De Jong ME, Van Tilburg SB, Nissen LHC, Kievit W, Nagtegaal ID, Horjus CS, *et al*. Long-term risk of advanced neoplasia after colonic low-grade dysplasia in patients with inflammatory bowel disease: a nationwide cohort study. *J Crohns Colitis* 2019; 13:1485–1491.
19 Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, *et al*. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005; 19(19 Suppl A):5A–36A.
20 Participants in the Paris W. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003; 58:S3–S43.
21 Altman DG. *Practical statistics for medical research*. Chapman and Hall; 1991.
22 Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation* 2016; 133:601–609.
23 Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 1988; 16:1141–1154.
24 Servier Medical Art. 2022. smart.servier.com.
25 Vieth M, Schubert B, Lang-Schwarz K, Stolte M. Frequency of Barrett's neoplasia after initial negative endoscopy with biopsy: a long-term histopathological follow-up study. *Endoscopy* 2006; 38:1201–1205.
26 Kiran RP, Ahmed Ali U, Nisar PJ, Khoury W, Gu J, Shen B, *et al*. Risk and location of cancer in patients with preoperative colitis-associated dysplasia undergoing proctocolectomy. *Ann Surg* 2014; 259:302–309.
27 Chappell R. Competing risk analyses: how are they different and why should you care? *Clin Cancer Res* 2012; 18:2127–2129.
28 Bertens LC, Broekhuizen BD, Naaktgeboren CA, Rutten FH, Hoes AW, van Mourik Y, *et al*. Use of expert panels to define the reference standard in diagnostic research: a systematic review of published methods and reporting. *PLoS Med* 2013; 10:e1001531.
29 Hulscher JBF, Haringsma J, Benraadt J, Offerhaus GJA, ten Kate FJW, Baak JPA, *et al*. Comprehensive Cancer Centre Amsterdam Barrett Advisory Committee: first results. *Neth J Med* 2001; 58:3–8.
30 Klaver E, van der Wel M, Duits L, Pouw R, Seldenrijk K, Offerhaus J, *et al*. Performance of gastrointestinal pathologists within a national digital review panel for Barrett's oesophagus in the Netherlands: results of 80 prospective biopsy reviews. *J Clin Pathol* 2021; 74:48–52.