SURVEILLANCE AND MANAGEMENT OF COLORECTAL NEOPLASIA IN INFLAMMATORY BOWEL DISEASE

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Surveillance and Management of Colorectal Neoplasia in Inflammatory Bowel Disease

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Surveillance and Management of Colorectal Neoplasia in Inflammatory Bowel Disease

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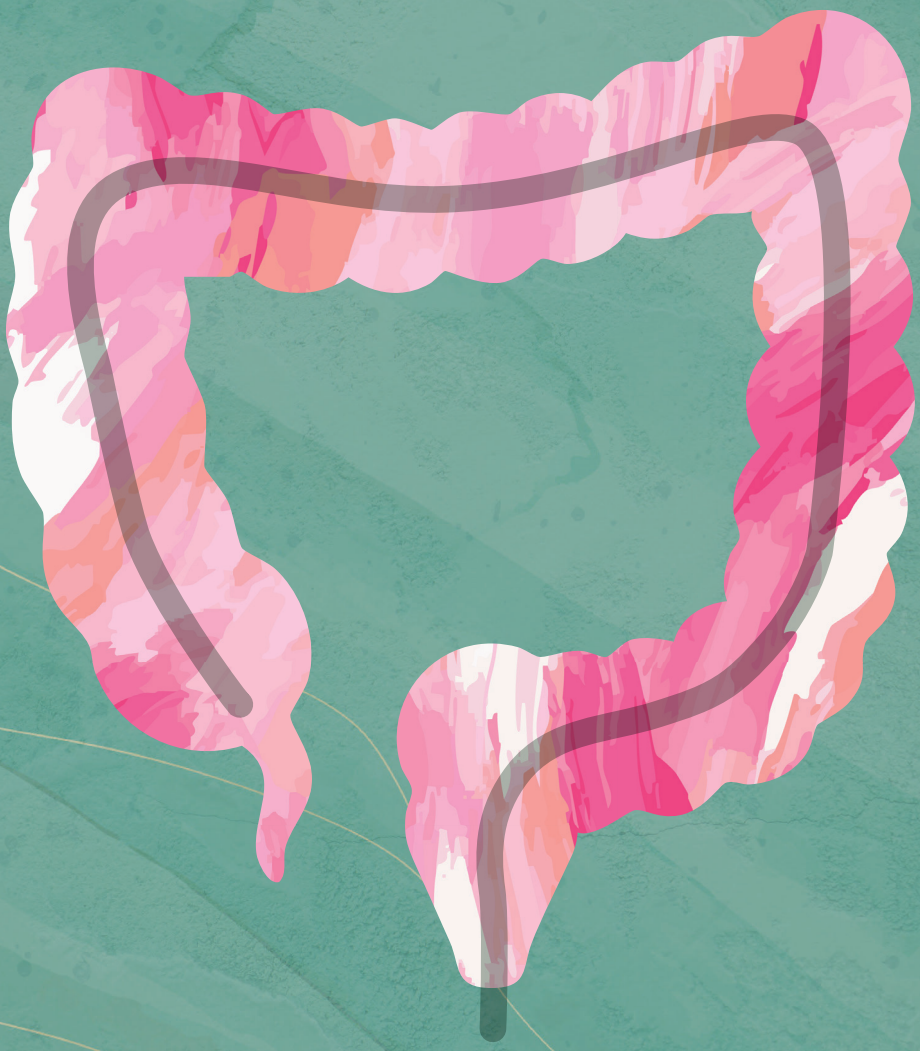

Chapter 1

General Introduction

In part adapted from:
Management of colorectal neoplasia in IBD patients: current practice and future perspectives

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Inflammatory bowel disease and colorectal neoplasia

Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract and includes Crohn's disease (CD) and ulcerative colitis (UC). IBD is characterized by a relapsing and remitting disease course. Symptoms may include abdominal pain, diarrhea, rectal blood loss, urgency, weight loss and fatigue. Moreover, IBD is associated with extra-intestinal manifestations such as arthritis, uveitis, erythema nodosum and primary sclerosing cholangitis (PSC) [1]. A combination of genetic susceptibility, environmental factors and the intestinal microflora result in an abnormal mucosal immune response that causes IBD [2,3]. Worldwide approximately seven million people are affected by IBD, with a rapid increasing incidence in developing countries [4,5]. The peak age of disease onset is 20-40 years [6]. IBD is treated with a wide range of anti-inflammatory medication and colorectal surgery to control disease activity and to prevent complications such as strictures, fistulae, abscesses and colorectal neoplasia (CRN).

It is widely accepted that chronic active inflammation is the main driver for IBD-associated CRN [7-9]. Although the CRC risk has decreased over time, IBD patients are still at a 1.4-1.7 times increased risk of developing CRC as compared to the general population [10-14]. CRN progresses gradually through various stages from low-grade dysplasia (LGD) to high-grade dysplasia (HGD) and finally colorectal cancer (CRC), resulting in morbidity and mortality (figure 1) [15]. The term indefinite for dysplasia (IND) is used if the distinction between neoplasia and non-neoplastic inflammatory changes is ambiguous [16]. Endoscopic surveillance is recommended by international guidelines in order to detect and remove CRN at an early stage [17-19].

CRN surveillance risk stratification

Patients with extensive disease, longer disease duration and younger age at IBD diagnosis are exposed to a potential high long-term inflammatory burden and consequently bear a high CRC risk [12,21-23]. Other risk factors include male sex, PSC and family history of CRC [24]. As a consequence, international guidelines recommend to perform a screening colonoscopy after 8-10 years of disease duration in all IBD patients, and in case of PSC directly following IBD diagnosis [17-19]. Subsequently, patients are stratified to annual, 2- to 3- or 5-yearly endoscopic surveillance based on the presence of risk factors (table 1). PSC is a chronic immune-mediated cholestatic liver disease characterized by inflammation and fibrosis of the biliary tract, that coincides with IBD in 70-90% of patients [25]. PSC-IBD patients have a 3-20 times higher

CRC risk as compared to IBD patients without PSC, and are therefore subjected to the highest CRC risk category with annual surveillance [26,27]. PSC-IBD is a distinct IBD phenotype, although underlying mechanisms remain unclear [28].

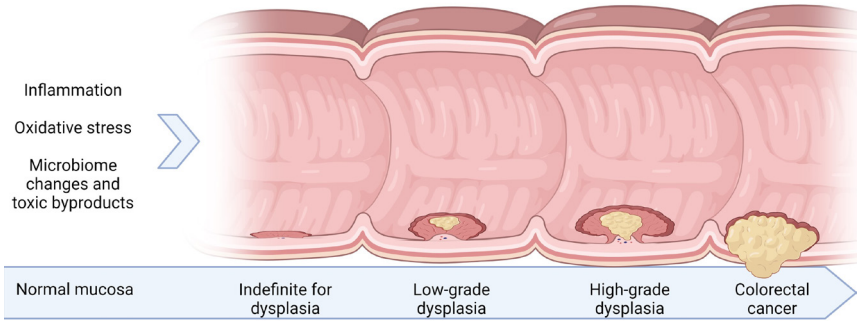

Figure 1. Stages of CRN development [20]

Table 1. Summary of surveillance guidelines' risk stratification

Guideline	Surveillance interval	Risk categories
British Society of Gastroenterology (BSG) 2019 [18]	• 5 years	**Low risk**: Left sided UC, CD <50% of the colon, extensive disease without active inflammation
	• 3 years	**Intermediate risk**: Extensive colitis with mild active inflammation, PIPs, CRC in FDR >50 years
	• 1 year	**High risk**: Extensive colitis with moderate/severe active inflammation, stricture (UC), dysplasia in prior 5 years, PSC, CRC in FDR <50 years
		No surveillance: Isolated ulcerative proctitis or ileal disease.
European Crohn's and Colitis Organisation (ECCO) 2022 [19]	• 5 years	**Low risk:** No intermediate or high risk factors
	• 2 or 3 years	**Intermediate risk**: Extensive colitis with mild to moderate active endoscopic and/or histological inflammation, CRC in FDR >50 years
	• 1 year	**High risk**: Extensive colitis with severe active endoscopic and/or histological inflammation, stricture (UC) in prior 5 years, dysplasia in prior 5 years, PSC, CRC in FDR ≤50 years
		No surveillance: Same as BSG
American Gastroenterological Association (AGA) 2021 [17]	• 5 years	**Low risk:** Continuous disease remission since last colonoscopy with mucosal healing on current exam, plus either of: ≥2 exams without dysplasia or minimal historical colitis (proctitis or <1/3 colon in CD)
	• 2 or 3 years	**Intermediate risk:** Mild inflammation (any extent), CRC in FDR <50, features of prior severe colitis, history of invisible dysplasia >5 years ago, history of lower risk visible dysplasia <5 years ago.
	• 1 year	**High risk:** Moderate or severe inflammation (any extent), PSC, CRC in FDR <50 years, dense PIPs, history of invisible or higher-risk visible dysplasia <5 years ago
		No surveillance: Isolated ileal disease.

UC: ulcerative colitis, CD: Crohn's disease, PIPs: post-inflammatory polyps, CRC: colorectal cancer, FDR: first degree relative, PSC: primary sclerosing cholangitis.

Diagnostic management

Surveillance techniques and quality indicators

Careful mucosal visualization is key to reducing the rate of missed lesions and effectively lower the CRC risk. Therefore, surveillance should ideally be performed during disease remission, since active inflammation may obscure subtle neoplastic changes [17,29,30]. In addition, sufficient bowel preparation and cecal intubation improve CRN detection rates [31,32]. New visualizing techniques such as high-definition equipment, dye-based (DCE) and virtual chromoendoscopy (VCE) may delineate otherwise invisible lesions. Since DCE results in longer procedural times, higher costs and reduced visualization in case of inflammation and suboptimal bowel preparation, high-definition white light endoscopy is often favored in clinical practice [33]. *The impact of surveillance quality indicators (e.g. interval, bowel preparation, active inflammation and cecal intubation) on CRN detection is uncertain.* Information on this may improve adherence to surveillance guidelines.

Endoscopic assessment

CRN may be categorized into visible and invisible lesions. The phenotype of visible lesions is generally assessed according to a modified Paris endoscopic classification of superficial neoplastic lesions, including polypoid (≥2.5 mm protruded; pedunculated or sessile) or non-polypoid (<2.5 mm protruded; completely flat, flat elevated, flat depressed), which together with the lesion diameter predicts the likelihood of CRN and submucosal invasion [34,35]. Invisible lesions are CRN lesions not visualized by endoscopists and are generally diagnosed in non-targeted biopsies or resection specimens.

Histopathology assessment

Histopathologic CRN assessment is performed on biopsies and resection specimen. Current understanding of carcinogenesis in IBD suggests that a lesion gradually progresses through the different CRN stages into CRC, rather than in clearly distinct categories. In addition, histopathological CRN diagnosis can be challenging to establish on a background of inflammatory or fibrotic changes, resulting in a high interobserver variability [36-39]. Consequently, international guidelines recommend that CRN should be confirmed by a second expert gastro-intestinal pathologist to improve diagnostic accuracy [17-19]. *The impact of histopathological revision on subsequent (advanced) CRN risk is unknown.*

Therapeutic management

Endoscopic resection

International guidelines recommend endoscopic resection if a suspected CRN lesion does not harbor stigmata of invasive growth and complete endoscopic resection can be achieved [17-19]. Low complexity lesions (<1cm, clearly delineated, without significant submucosal fibrosis) can be treated with standard cold-snare polypectomy [40-42]. However, resection of CRN in IBD patients is often challenging due to non-polypoid morphology, submucosal fibrosis caused by chronic inflammation and unclear borders due to active inflammation. These complex lesions (≥1cm, laterally spreading, highly irregular, indistinct borders) should be treated with advanced polypectomy techniques such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), with a higher likelihood of complete and *en bloc* resection. EMR involves creating a submucosal cushion through injection of fluid (i.e. saline or methylene blue) into the submucosa via a needle catheter followed by snare resection, either *en bloc* or piecemeal. In ESD, a lesion is lifted from the muscularis propria and dissected from deeper layers. Two recent meta-analysis reported a low CRC risk of 2 per 1000 patient-years after endoscopic CRN resection in IBD [43,44]. Only one study researched this for advanced CRN (i.e. HGD and CRC) and found no statistical difference in metachronous CRN after endoscopic resection of HGD compared to LGD [45].

Surgical resection

Historically, a proctocolectomy or (sub)total colectomy was recommended for advanced CRN or endoscopically unresectable CRN, due to the high risk of synchronous and metachronous lesions. Synchronous CRN is defined as co-existence of two or more neoplastic colorectal lesions. Metachronous CRN is defined as sequential CRN detected after treatment of the index lesion. Advances in endoscopic techniques have improved CRN detection and enabled a more restrictive surgical approach using partial colectomy [46-49]. Hence, more recent British and European guidelines advise a tailored treatment strategy with the consideration of partial colectomy in a subgroup of patients [18,50,51]. One recent study in CD patients with CRC and mostly ileal disease reported no increased metachronous CRC risk after partial colectomy as compared to (sub)total or proctocolectomy [46]. Another study in UC patients with CRC showed no metachronous CRC after 7 years of follow-up, suggesting partial colectomy might be feasible in elderly patients [47]. *However, large-scale data on patients with extensive colonic disease are lacking.*

Surveillance after CRN treatment

Surveillance after complete endoscopic or surgical resection of visible CRN

After complete endoscopic resection of CRN, international guidelines advocate a shortened surveillance interval of 3-6, 12 or 24 months, depending on the lesion size, complexity and grade [17-19] (Table 2). These recommendations are based on the high subsequent risk of synchronous and metachronous CRN [43,44,52].

Table 2. Guideline recommendations for surveillance strategy after CRN

Guideline	CRN risk classification	Intensified surveillance interval
British Society of Gastroenterology (BSG) 2019 [18]	Invisible CRN or incomplete resection	• Not specified
	CRN in the past 5 years	• 1 year
European Crohn's and Colitis Organisation (ECCO) 2022 [19]	Invisible CRN, multifocal CRN, HGD	• 3 months for the first year
	Non-polypoid LGD	• 6 months for the first year
	Polypoid <1 cm or peduncled LGD, IND	• 1 year
American Gastroenterological Association (AGA) 2021 [17]	**High risk**: (invisible) HGD; incomplete resection; large size (≥ 2cm), complex (lateral spreading, highly irregular, indistinct border) LGD	• 3-6 months for the first year
	Medium risk: (Invisible) LGD; medium size (1-2cm) LGD; high or medium risk CRN <5 years ago	• 1 year
	Low risk: small (< 1cm) or peduncled LGD (2 years); low risk CRN <5 years ago; high or medium risk CRN >5 years ago	• 2-3 years

CRN: colorectal neoplasia, HGD: high-grade dysplasia, LGD: low-grade dysplasia.

Since prospective studies to determine surveillance intervals are lacking, it is challenging to make recommendations on how long an intensified (3-6 months) surveillance strategy after CRN detection should be maintained, before switching to annual surveillance. The AGA guideline recommends continuing until two consecutive negative high-quality surveillance colonoscopies with dye-based inspection is reached, while the ECCO guideline recommends continuing this intensified strategy for one year [17,19]. Moreover, all guidelines advise to continue surveillance based on the highest risk classification, which is annual surveillance for 5 years after CRN detection, particularly invisible or high-risk CRN [17-19].

Healthcare utilization

IBD healthcare depends on frequent outpatient monitoring, including regular endoscopic follow-up, and surgical procedures in case of IBD complications. The COVID-19 pandemic challenged IBD healthcare networks, with a reduced hospital capacity for non-COVID-19 care. Measures such as telemedicine and improved procedure triage were installed to restore IBD healthcare utilization. *Exact consequences of these measures are unknown.* Cancellation or postponement of surveillance endoscopies and surgery may have caused LGD progression to advanced CRN (HGD or CRC), with potential negative impact on morbidity and mortality. Information on this could aid healthcare policy makers with decision making in the future.

Aims of this thesis

The ultimate goal of endoscopic surveillance in IBD is to reduce the risk of CRN-related morbidity and mortality. The aims of this thesis are:

1. To evaluate quality of endoscopic surveillance and its impact on CRN risk
2. To assess effectiveness of endoscopic treatment versus surgery
3. To determine IBD healthcare utilization during the COVID-19 pandemic

Outline

In **part I** we focused on surveillance quality indicators and CRN diagnosis. In **chapter 2** we assessed the impact of compliance with surveillance quality indicators on CRN risk in a multicenter case-control study. Quality indicators included surveillance interval, active inflammation, cecal intubation, and bowel preparation. In **chapter 3** we evaluated the impact of histopathological revision and expert pathologist consensus of HGD diagnosis in a multicenter retrospective cohort study. Outcomes were diagnostic accuracy and metachronous CRN risk.

In **part II** we assessed CRN therapeutic management and follow-up. In **chapter 4** we performed a multicenter retrospective cohort study to assess synchronous and metachronous CRN risk and mortality following different treatment modalities of advanced CRN (HGD and CRC). Treatment modalities were categorized as endoscopic treatment, partial colectomy, and (sub)total or proctocolectomy. In

chapter 5 we assessed the risk of CRC after initial HGD diagnosis in a nationwide retrospective cohort study.

In **part III** we focused on IBD healthcare utilization during the COVID-19 pandemic. In **chapter 6** we assessed the impact of COVID-19 on new IBD diagnosis, IBD related endoscopies, surgery and CRN diagnoses during the first COVID-19 peak in the Netherlands in a nationwide retrospective cohort study. **Chapter 7** provides a two-year nationwide update.

Chapter 8 provides a general discussion on the results of this thesis and implications for CRN surveillance and management in clinical practice.

Table 2. Summary of aims and methodology

Chapter	Aim(s)	Design	Cohort/Methodology
1	To provide an up-to-date overview and future perspectives on CRN management and the subsequent surveillance strategies in IBD patients	Narrative review	Narrative review
Part I: Surveillance and diagnosis			
2	To determine the impact of surveillance quality indicators on advanced CRN risk	Multicenter case-control study	Nationwide pathology databank search (PALGA) Multivariable logistic regression model with Firth's correction
3	To evaluate pathologist inter-observer variability for HGD in IBD To assess the impact of revision and expert pathologist consensus on metachronous CRN risk	Multicenter retrospective cohort study	Nationwide pathology databank search (PALGA) Cohen's kappa Cumulative incidence functions with Gray's tests
Part II: Treatment and follow-up			
4	To compare synchronous and metachronous CRN risk and mortality following endoscopic resection, partial colectomy, and (sub)total or proctocolectomy for advanced CRN To determine associations with treatment modalities	Multicenter retrospective cohort study	Nationwide pathology databank search (PALGA) Fine & Gray's subdistribution hazard model Multinomial logistic regression
5	To determine the long-term risk of CRC after HGD To identify risk factors for progression to CRC To provide trends in treatment strategies over the past three decades	Nationwide retrospective cohort study	Nationwide pathology databank search (PALGA) Cumulative incidence functions Multivariable logistic regression
Part III: Healthcare utilization			
6	To determine IBD healthcare utilization during the COVID-19 pandemic	Nationwide retrospective cohort study	Nationwide pathology databank search (PALGA) Incidence graphs with reduction rates compared to 2018-2019
7	To assess the impact of consecutive COVID-19 waves on IBD healthcare utilization deficits during the first 2-years of the COVID-19 pandemic	Nationwide retrospective cohort study	Nationwide pathology databank search (PALGA) Incidence graphs with reduction rates compared to 2018-2019

CRN: colorectal neoplasia, IBD: inflammatory bowel disease, PSC: primary sclerosing cholangitis, CRC: colorectal cancer, HGD: high-grade dysplasia, COVID: coronavirus disease

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Part I

Surveillance and diagnosis

Chapter 2

Quality of surveillance impacts the colitis-associated advanced neoplasia risk: a multicenter case-control study

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Abstract

Background and aims

Although colorectal cancer (CRC) surveillance is embedded in clinical inflammatory bowel disease (IBD) practice, a subset of patients still develops advanced neoplasia (AN) (high-grade dysplasia [HGD] and/or CRC). We aimed to assess the impact of surveillance quality on AN risk in IBD.

Methods

In this multicenter case-control study, we searched the Dutch nationwide pathology databank to identify IBD cases with AN and controls with indefinite or low-grade dysplasia. The surveillance colonoscopy preceding the index lesion (first indefinite for dysplasia [IND]/low-grade dysplasia [LGD] or AN) was used to assess the impact of surveillance quality. We assessed intervals, bowel preparation, cecal intubation, and absence of inflammation as primary quality indicators. In addition, we assessed chromoendoscopy, endoscopist expertise, hospital setting, and biopsy strategy. Associations of quality indicators with AN risk were determined with multivariable logistic regression analyses with Firth's correction.

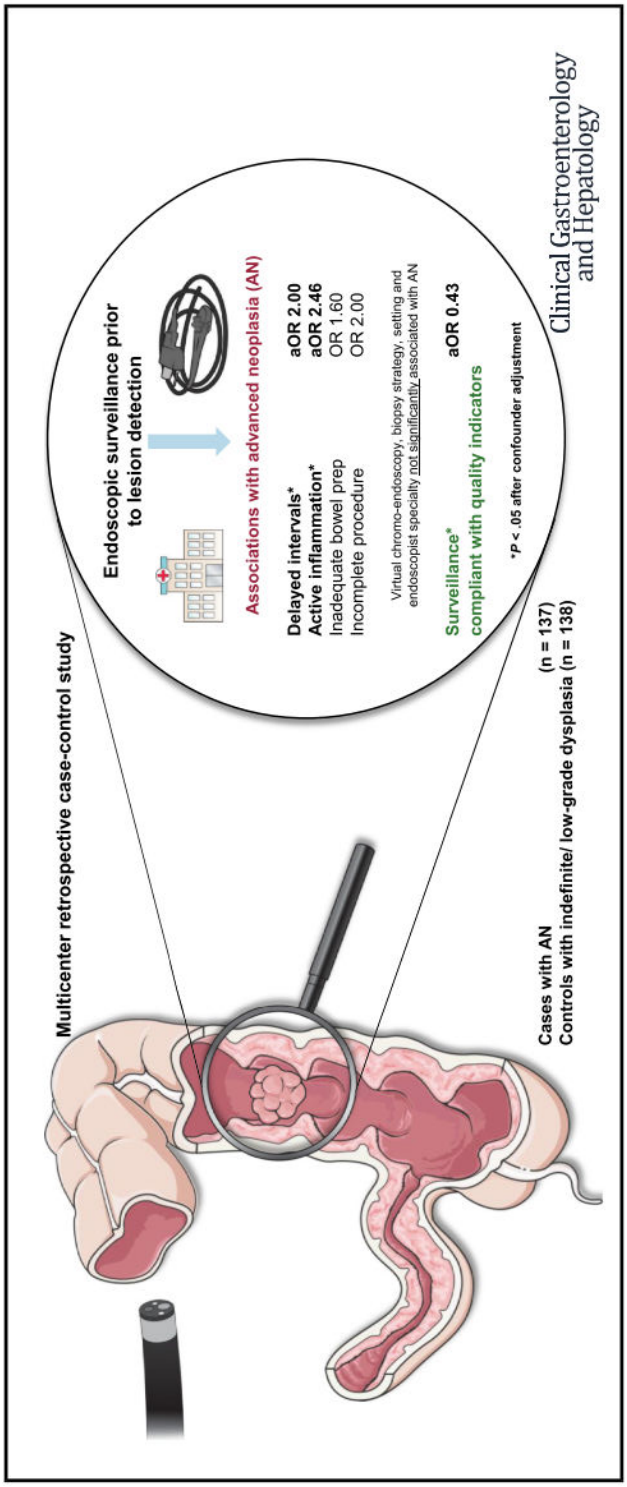
Results

We included 137 cases and 138 controls. Delayed intervals (58.2% vs 39.6%) and active inflammation (65.3% vs 41.8%) were frequently present in cases and controls and were associated with AN (delayed interval: adjusted odds ratio [aOR], 2.00; 95% confidence interval [CI], 1.07–3.81; P [.03; active inflammation: aOR, 2.46; 95% CI, 1.33–4.61; P <.01). Surveillance compliant with primary quality indicators was associated with a reduced AN risk (aOR, 0.43; 95% CI, 0.22–0.91; P [.03), similar to chromoendoscopy (OR, 0.11; 95% CI, 0.01–0.89; P [.01). Other indicators were not significantly associated with AN.

Conclusions

Surveillance compliant with primary quality indicators is associated with a reduced colitis-associated AN risk. Delayed surveillance intervals and active inflammation were associated with an increased AN risk. This underlines the importance of procedural quality, including endoscopic remission to optimize the effectiveness of endoscopic surveillance.

Keywords: colitis, colon, Crohn's, dysplasia, screening


Multicenter retrospective case-control study
Cases with AN (n = 137)
Controls with indefinite/ low-grade dysplasia (n = 138)
Endoscopic surveillance prior to lesion detection
Associations with advanced neoplasia (AN)
Delayed intervals* aOR 2.00
Active inflammation* aOR 2.46
Inadequate bowel prep OR 1.60
Incomplete procedure OR 2.00
Virtual chromo-endoscopy, biopsy strategy, setting and endoscopist specialty not significantly associated with AN
Surveillance* compliant with quality indicators aOR 0.43
*P < .05 after confounder adjustment
Clinical Gastroenterology and Hepatology

Introduction

Patients with inflammatory bowel disease (IBD) bear an increased risk of advanced neoplasia (AN) (including high-grade dysplasia [HGD] and colorectal cancer [CRC]) compared with the general population.[1-3] Endoscopic surveillance is recommended to attenuate this risk by detection and removal of dysplastic precursor lesions, including indefinite for dysplasia (IND) and low-grade dysplasia (LGD).[4,5] Despite current surveillance strategies, a significant number of IBD patients develops AN, resulting in morbidity and mortality.[5,6]

Endoscopic surveillance is widely implemented in daily IBD practice, although underlying evidence for its effectiveness is limited.[5,7] Development of AN can be used as a surrogate marker for effectiveness of endoscopic surveillance. Indeed, one meta-analysis concluded that endoscopic surveillance reduced CRC risk but was limited by a lack of information on quality of endoscopic surveillance.[5] High-quality surveillance is essential to ensure optimal mucosal visualization and prevent missed precursor lesions that may develop into AN.[8,9]

Although multiple studies have highlighted surveillance characteristics and performance in IBD, data regarding the effect of quality indicator compliance on surveillance effectiveness remain limited.[8] A recent study suggested that active inflammation might impede mucosal visualization of lesions,[10] although the exact impact of this limitation is unknown. Sufficient bowel preparation and cecal intubation are also relevant factors impacting mucosal visualization.[8,9] Endoscopic technique (white light vs chromoendoscopy), biopsy strategy (random and/or targeted biopsies), hospital setting (academic or community), and endoscopist expertise may impact the quality of surveillance as well.[11-13] Finally, surveillance intervals (CIs) are determined by risk stratification and delayed procedures may result in preventable interval AN.[14]

We hypothesized that reduced quality of endoscopic surveillance in IBD patients is associated with increased AN risk. In order to test this hypothesis, we designed a multicenter case-control study evaluating surveillance quality indicators and associated AN risk in IBD patients.

Materials and Methods

Study Design

We performed a retrospective multicenter case-control study to evaluate the impact of surveillance quality on the risk of AN (HGD or CRC) in IBD, with assessment of compliance to individual quality indicators including interval adequacy, bowel preparation, cecal intubation, and presence of active inflammation. Moreover, we assessed the impact of chromoendoscopy, biopsy strategy, hospital setting, and type of endoscopist.

Cases were patients with IBD and AN, as prevention of AN is one of the aims of endoscopic surveillance. Controls were patients with IBD and IND or LGD. We assumed that these controls with IND or LGD, rather than patients with IBD without dysplasia, would have intermediate to high AN risk profiles that are similar to cases. This provides a methodological setting that allows for a comparison of surveillance quality between higher-risk groups.

Patients

We searched the Dutch Nationwide Pathology Databank (PALGA) (Izv2019-87)[15] to identify IBD patients with IND, LGD, HGD, or CRC. PALGA has complete national coverage of both academic and nonacademic hospitals since 1991, with good accuracy in IBD.[16] All reports have a unique hash that allows identification of individual patients through electronic patient records. We performed a search combining search terms for IBD ("ulcerative colitis", "Crohn's disease", "indeterminate colitis", "chronic idiopathic inflammatory bowel disease") and for neoplasia ("indefinite for dysplasia", "low-grade dysplasia", "high-grade dysplasia", "carcinoma in situ", and "colorectal cancer"), located in the colon or rectum. Reports from January 1, 1991, to December 1, 2020, were collected.

All cases and controls from 5 academic and 2 community hospitals (with a cohort of 1923–3000 IBD patients),[17] were included if they fulfilled the following criteria: (1) an established histological diagnosis of colonic IBD (ulcerative colitis [UC], Crohn's disease [CD], or IBD unclassified), (2) a histological diagnosis of colorectal IND or LGD without AN (controls) or AN (cases), and (3) with available clinical and endoscopic data. Exclusion criteria comprised (1) familial CRC syndromes; (2) IND, LGD, or AN before IBD diagnosis; and (3) no indication for continued surveillance according to the British Society of Gastroenterology (BSG) 2019 guideline (ulcerative proctitis or <8 years of IBD in absence of primary sclerosing cholangitis [PSC]).[4]

Quality Assessment

Surveillance quality was primarily assessed by (1) surveillance intervals and (2) mucosal visualization, including bowel preparation, cecal intubation and presence of active inflammation. Secondary assessment included chromoendoscopy, biopsy strategy, hospital setting, and endoscopist expertise as potential quality indicators.

We used the last surveillance colonoscopy prior to index lesion (defined as first IND or LGD in controls or AN in cases) to assess the impact of quality indicators. We considered procedures as surveillance if they (1) were elective colonoscopies and (2) were not scheduled for assessment of (suspected) disease activity or therapeutic measures. In case only non-surveillance endoscopies were performed prior to index lesion detection, this was considered as absence of surveillance.

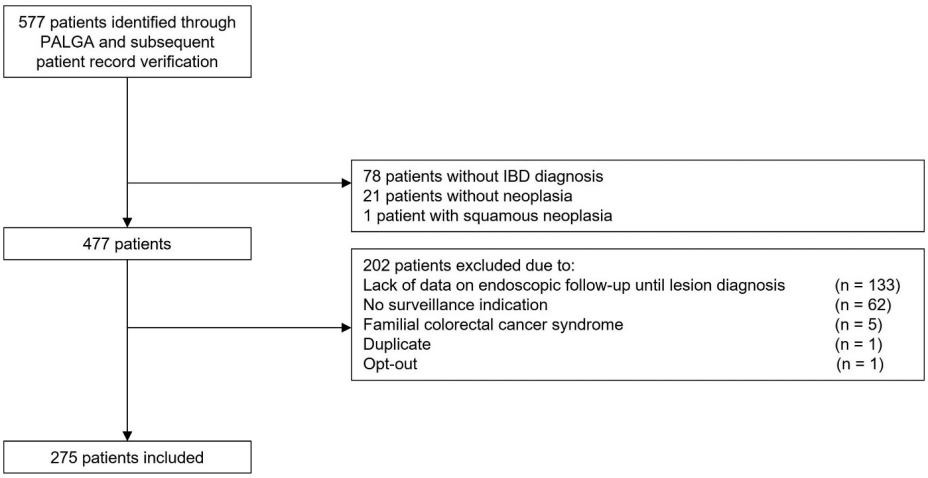


Figure 1. Patient identification.

Table 1. Baseline characteristics of cases and controls

Characteristics	Cases (AN) (n=137)	Controls (IND/ LGD) (n=138)	p-value
Male sex, n [%]	78 [56.9]	80 [58.0]	0.860
Disease, n [%]			
Ulcerative colitis	85 [62.0]	103 [74.6]	0.079
Crohn's disease	47 [34.3]	32 [23.2]	
IBD-unclassified	5 [3.6]	3 [2.2]	
Age at IBD diagnosis, median [IQR]	30.0 [20.0-41.0]	34.0 [27.0-45.0]	0.004[a]
Disease duration, median [IQR]	20.0 [15.0-28.0]	18.5 [13.8-27.0]	0.189
Maximal endoscopic disease extent (Montreal), n [%]			
E2 (ulcerative colitis)	16 [11.7]	44 [31.9]	0.000[a]
E3 (ulcerative colitis)	74 [54.0]	56 [40.6]	
<50% (Crohn's disease)	15 [10.9]	22 [15.9]	
>50% (Crohn's disease)	32 [23.4]	16 [11.6]	
Maximal histological disease extent (Montreal), n [%][b]			
E2 (ulcerative colitis)	12 [8.8]	26 [18.8]	0.000[a]
E3 (ulcerative colitis)	69 [50.4]	37 [26.8]	
<50% (Crohn's disease)	14 [10.2]	53 [38.4]	
>50% (Crohn's disease)	30 [21.9]	22 [15.9]	
Disease behavior (Crohn's disease; Montreal), n [%]			
B1	11 [23.4]	22 [66.7]	0.001[a]
B2	13 [27.7]	6 [18.2]	0.117
B3	8 [17.0]	1 [3.0]	
B2+3	15 [31.9]	4 [12.1]	
P	19 [13.9]	11 [8.0]	
For ulcerative colitis/IBD-unclassified: stricture, n [%]	22 [22.4]	11 [10.5]	0.011[a]
Guideline colorectal cancer risk stratification, n [%]			
Low	29 [21.2]	62 [44.9]	0.000[a]
Intermediate	42 [30.7]	43 [31.2]	
High	66 [48.2]	33 [23.9]	
Family history of colorectal cancer, n [%]			
Yes	20 [14.6]	18 [13.0]	0.709
No or unknown	117 [85.4]	120 [87.0]	
Smoking, n [%] [c]			
Yes	5 [4.5]	13 [9.4]	0.045[a]
No or stopped	106 [77.4]	96 [69.6]	
Primary sclerosing cholangitis, n [%]	18 [13.1]	15 [10.9]	0.563
Post-inflammatory polyps, n [%]	74 [54.0]	67 [48.6]	0.365
Medication history, n= [%]			
Aminosalicylates	65 [48.5]	98 [71.5]	0.000[a]
Thiopurines / Methotrexate	28 [20.4]	55 [39.9]	0.000[a]
Biologicals/small molecules	10 [7.5]	27 [19.7]	0.004[a]

AN, advanced neoplasia; CD, Crohn's disease; IBD, inflammatory bowel disease; IND, indefinite for dysplasia; LGD, low-grade dysplasia; UC, ulcerative colitis.

[a] P <.05, [b] 38 missing values, [c] 55 missing values

Definitions of Quality Indicators

Considering the 2019 BSG guideline as a best-practice framework for surveillance, we assessed the following primary quality indicators by 2 researchers (M.t.G. and M.D.)[4]:

1. Surveillance intervals. Based on clinical CRC risk factors, the BSG guideline stratifies patients to a surveillance interval of 1, 3, or 5 years (Supplementary Figure 1). The start point of surveillance is 8 years after IBD diagnosis. In case of PSC, annual surveillance after IBD diagnosis is recommended. If the recommended surveillance interval was exceeded by more than a 3-month margin, we considered this a delayed interval.
2. Insufficient bowel preparation, defined as a Boston Bowel Preparation Scale score <6 and/or based on the endoscopists judgement as described in the endoscopy report. We classified the bowel preparation (if Boston Bowel Preparation Scale score was not reported) as insufficient if termed in the endoscopy report as insufficient, poor, or inadequate or if a repeat colonoscopy was requested due to bowel preparation.
3. Incompleteness of surveillance, defined as absence of cecal intubation.
4. Presence of endoscopic inflammation. Depending on the analysis, we assessed the impact of the presence or absence of (1) any grade and extent of active inflammation, (2) only moderate-to-severe inflammation, or (3) exclusion of E1 colitis patients on the AN risk. For each procedure the maximum endoscopic severity of inflammation in any colonic segment was scored using an ordinal score (normal/inactive = 1, mild = 2, moderate = 3, severe = 4) as previously published.[18] In case of hybrid descriptors (e.g. moderate to severe) the maximum grade was recorded.

Secondary quality indicators included the following:

1. Endoscopic technique (chromoendoscopy, defined as dye-based or virtual chromoendoscopy vs white light endoscopy).
2. Biopsy strategy (targeted biopsies only vs random biopsies only or both).
3. Hospital setting (community vs academic hospital).
4. Expertise of the endoscopist (IBD specialist, gastroenterologist without IBD specialty, or resident).

Data Collection

We extracted the following data from the electronic patient files: sex, age, IBD type and behavior, disease duration, and maximum endoscopic and histologic IBD extent (UC: according to the Montreal classification; CD: more or less than 50% inflamed colonic mucosa).[19] Extensive disease was defined as E3 colitis for UC and >50%

inflamed colonic mucosa for CD. Furthermore, we extracted data on index lesion characteristics (visible vs invisible, resection status), CRC family history, smoking status, PSC, and post-inflammatory polyps. Data on all endoscopic procedures up to index lesion were collected, including date, type, and indication (surveillance vs other).

Statistical Analysis

Continuous outcomes were reported as median (interquartile range [IQR]) and categorical outcomes were reported as frequency and proportion. Differences between groups were assessed with the chi-square test, Student's t test, or nonparametric alternatives when appropriate. The impact of endoscopic quality indicators and surveillance intervals on AN risk was assessed employing a multivariable logistic regression model with Firth's correction to minimize low observation bias.[20] Selection of confounders was based on literature[21] and a study group consensus meeting and are displayed in a diagram, a priori developed in DAGitty (Supplementary Figure 2).[22] We attempted to account for the inherent AN risk associated with active inflammation (recorded as presence or absence) by adjustment for disease extent and endoscopic cumulative inflammatory burden score, and for this purpose we included all colonoscopies before index lesion detection (Supplementary Figure 3).[23] We performed multiple sensitivity analyses to assess the robustness of our methodology and results, including (1) colonoscopies with any type of indication (surveillance and other) and (2) only index lesions diagnosed after introduction of high-definition colonoscopes in 2005[24] or (3) after implementation of the first Dutch surveillance guideline in 2008.[25] Effects were presented as odds ratio (OR) and adjusted OR (aOR) with 95% CI. A 2-tailed P value of <.05 was considered statistically significant. All analyses were performed using SPSS v25 (IBM Corporation, Armonk, NY) and R (v3.5.3, package *logistf*; R Foundation for Statistical Computing, Vienna, Austria).

Ethical Considerations

This study was approved by the institutional review board of Radboud University Medical Center (2017–3219) and the scientific committee of PALGA.

Results

Baseline Characteristics

We included 275 patients with IBD (Figure 1), including 137 cases with AN (CRC: n = 78 [56.9%]; HGD: n = 59 [43.1%]) and 138 controls with LGD (n = 133 [96.4%]) or IND (n = 5 [3.6%]). Lesion characteristics are reported in Supplementary Table 1.

Cases with AN were diagnosed with IBD at a younger age (30.0 [IQR, 20.0–41.0] years vs 34.0 [IQR, 27.0–45.0] years; P <.01) and more frequently had extensive disease (77.4% vs 52.2%; P <.01) (Table 1). They more often had penetrating and stricturing CD (75.6% vs 34.4%; P <.01), strictures in UC (22.4% vs 10.5%; P =.01), and a high CRC risk stratification according to the 2019 BSG guidelines (48.2% vs 23.9%; P <.01).4 Furthermore, cases had a higher cumulative inflammatory burden score (median 14.5 [IQR, 6.2–25.9] vs 8.8 [IQR, 2.9–20.9]; P <.01).

The number of endoscopic procedures and follow-up time until the index lesion were similar between cases and controls (4 [IQR, 2–6] procedures vs 4 [IQR, 2–5] procedures; P =.19 and median 9 [IQR, 6–14] years vs 10 [IQR, 7–14] years; P =.30).

Quality Indicators

Patients frequently underwent endoscopic surveillance with delayed intervals (cases: 58.2% vs controls: 39.6%; P =.01) or active inflammation (cases: 65.3% vs controls: 41.8%; P <.01) (Figure 2). Insufficient bowel preparation was observed in 4.1% vs 5.5% of cases and controls, respectively (P =.53). Incomplete procedures were reported in 5.1% of cases vs 5.5% of controls (P =.92). Fourteen (14.3%) cases vs 27 (29.7%) controls (P =.04) underwent endoscopic surveillance compliant with primary quality indicators prior to index lesion. This rate was similar between HGD and CRC cases (8.6% vs 10.3%; P =.43). By contrast, absence of any endoscopic surveillance until index lesion was observed in 27.7% of cases vs 31.2% of controls (P =.39) (Supplementary Table 2). No neoplasia was detected during the procedure that diagnosed IBD.

Dye-based chromoendoscopy was performed in 8 (8.8%) controls and 1 (1.0%) case during the surveillance colonoscopy prior to index lesion detection (P =.01) (Supplementary Table 3). Virtual chromoendoscopy was used in 4 (5.1%) cases and 4 (6.1%) controls (P =.79). There were no significant differences in biopsy strategy (random biopsies 67.5% vs 74.7%; P =.33) or number of random biopsies (median 20.5 [IQR, 9.8–27.0] vs 22.0 [IQR, 11.0–27.5]; P =.61) between cases and controls. In line, we did not observe differences in hospital setting (academic 78.6% vs 84.6%;

P =.29) or endoscopist expertise (IBD specialist 29.5% vs 38.0%; P ¼.33) between cases and controls, respectively.

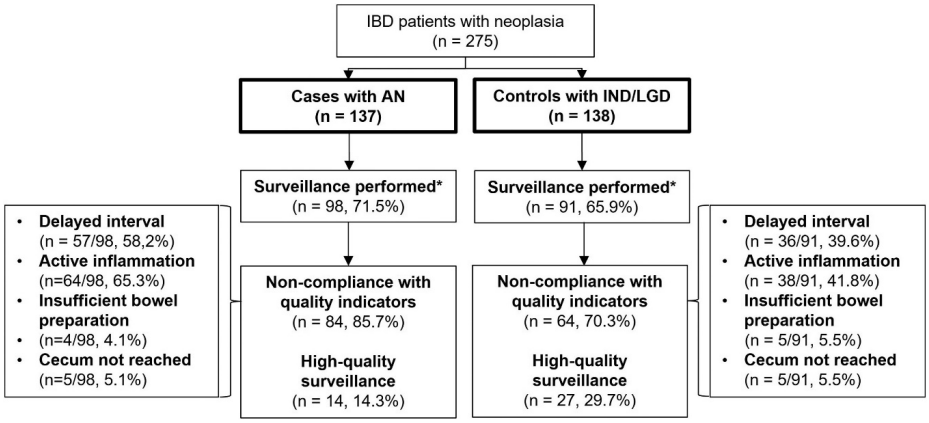


Figure 2. Surveillance enrollment showing absolute frequencies of primary quality indicator compliance. *Patients without surveillance had nonsurveillance colonoscopies prior to index lesion detection or lesions detected during the screening colonoscopy without a previous surveillance indication (Supplementary Table 2).

Table 2. Regression results for the associations between non-compliancy with quality indicators with AN risk.

	OR (95% CI)	p-value
Quality indicators – unadjusted		
Primary[a]		
Delayed interval	3.24 (1.47-7.14)	<0.01[b]
Insufficient bowel preparation	1.60 (0.37-6.99)	0.53
Incomplete procedure	2.00 (0.49-8.17)	0.33
Active inflammation	3.37 (1.55-7.33)	<0.01[b]
Secondary		
Dye-based chromo-endoscopy (vs white light)	0.11 (0.01-0.89)	0.01[b]
Virtual chromo-endoscopy (vs white light)	1.21 (0.29-5.04)	0.79
Targeted biopsies only (vs random/both)	1.42 (0.71-2.85)	0.33
Academic hospital (vs community)	0.67 (0.32-1.40)	0.29
IBD-specialist (vs resident under supervision)	0.69 (0.33-1.46)	0.33
	aOR (95% CI)	**p-value**
Quality indicators - adjusted		
Delayed interval[c]	2.00 (1.07-3.81)	0.03[b]
Active inflammation[d]	2.46 (1.33-4.61)	<0.01[b]
Excluding patients with E1 colitis	2.45 (1.30-4.68)	<0.01[b]
Excluding patients with mild inflammation	3.71 (1.73-8.25)	<0.01[b]

Table 2. Continued

	OR (95% CI)	p-value
Surveillance - adjusted		
Surveillance compliant with all primary quality indicators[e]	0.43 (0.20-0.91)	0.03[b]
Irrespective of active inflammation	0.44 (0.20-0.98)	0.04[b]
Irrespective of inflammatory burden score[f]	0.38 (0.17-0.78)	0.01[b]
Surveillance irrespective of compliancy with quality indicators[3]	0.90 (0.51-1.59)	0.71
Sensitivity analyses		
Colonoscopies with any type of indication		
Delayed interval[c]	1.87 (0.99-3.59)	0.05
Active inflammation[d]	2.69 (1.20-6.20)	0.02[b]
Surveillance compliant with all primary quality indicators[e]	0.43 (0.20-0.90)	0.03[b]
After implementation of HD-colonoscopes		
Delayed interval[c]	1.93 (1.03-3.65)	0.04[b]
Active inflammation[d]	2.33 (1.25-4.37)	0.01[b]
Surveillance compliant with all primary quality indicators[e]	0.45 (0.20-0.95)	0.04[b]
After implementation of the first Dutch surveillance guideline		
Delayed interval[c]	2.02 (1.06-3.90)	0.03[b]
Active inflammation[d]	2.15 (1.14-4.12)	0.02[b]
Surveillance compliant with all primary quality indicators[e]	0.44 (0.20-0.94)	0.04[b]

aOR, adjusted odds ratio; CI, confidence interval; HD, high-definition; IBD, inflammatory bowel disease; OR, odds ratio.

[a] versus surveillance compliant with all other primary quality indicators

[b] P <.05

[c] adjusted for active inflammation, age at IBD diagnosis, CRC family history, PSC, extensive disease, cumulative inflammatory burden and strictures as covariates.

[d] adjusted for extensive disease, strictures, cumulative inflammatory burden score and delayed interval.

[e] same as model 1, without active inflammation as covariate.

[f] same as model 1, without active inflammation and cumulative inflammatory burden as covariate

Impact of Surveillance Quality on AN Risk

Delayed surveillance intervals were associated with an increased AN risk (aOR, 2.00; 95% CI, 1.07–3.81; P =.03) (Table 2). The median surveillance delay did not differ between cases and controls (median 26.0 [IQR, 14.0–41.5] months vs 27.5 [IQR, 13.8–44.0] months; P =.50). The presence of active inflammation resulted in an increased AN risk (aOR, 2.46; 95% CI, 1.33–4.61; P <.01) (Table 2). Exclusion of patients with active E1 colitis or only mild inflammation resulted in a similar AN risk (Table 2). Cases had more often extensive disease (34.7% vs 16.5%; P <.01) and severe active inflammation (20.6% vs 3.3%; P <.01) compared with controls (Table 3). Dye-based chromoendoscopy resulted in a reduced AN risk (OR, 0.11; 95% CI, 0.01–0.89; P =.01). By contrast, insufficient bowel preparation, incomplete procedures, virtual chromoendoscopy, targeted only biopsies, hospital setting, and endoscopist expertise were not significantly associated with AN (Table 2). Patients who received endoscopic surveillance compliant with all primary quality indicators had a significantly lower risk of AN (aOR, 0.43; 95% CI, 0.22–0.91; P ¼.03). However,

if surveillance irrespective of compliance with quality indicators was assessed, no significant effect on AN was found (aOR, 0.90; 95% CI, 0.51–1.59; P =.71).

Table 3. Extent and severity of active inflammation at last surveillance colonoscopy prior index lesion diagnosis and endoscopic cumulative inflammatory burden score

	Cases (AN) (n=98)	Controls (IND/LGD) (n=91)	P-value
Severity[a]			
Inactive disease (1)	32 [32.7]	52 [57.1]	<0.01[b]
Mild inflammation (2)	20 [20.6]	25 [27.5]	
Moderate inflammation (3)	24 [24.5]	10 [10.9]	
Severe inflammation (4)	20 [20.6]	3 [3.3]	
Extent[c]			
E1	7 [7.7]]	6 [6.6]	<0.01[b]
E2	12 [12.3]	11 [12.1]	
E3	23 [23.7]	14 [15.4]	
<50% (CD)	10 [10.3]	5 [5.5]	
>50% (CD)	11 [11.3]	1 [1.1]	
Endoscopic cumulative inflammatory burden score, median [IQR]	14.5 [6.2-25.9]	8.8 [2.9-20.9]	<0.01[b]

AN, advanced neoplasia; CD, Crohn's disease; IND, indefinite for dysplasia; LGD, low-grade dysplasia.

[a] 3 missing values

[b] P <.05

[c] 2 missing values

Sensitivity Analyses

Results from the sensitivity analyses showed effect sizes in line with the main analyses. If colonoscopies with any type of indication (surveillance and other) were considered, delayed intervals resulted in a non-significantly increased AN risk (aOR, 1.87; 95% CI, 0.99–3.59; P =.054) (Table 2). Similarly, active inflammation was associated with a significantly increased AN risk (aOR, 2.69; 95% CI 1.20–6.20; P =.02). Exclusion of patients with an index lesion before introduction of high-definition surveillance or the first Dutch surveillance guideline showed increased ORs consistent with the main analyses (Table 2).

Discussion

In this multicenter case-control study including 275 patients with IBD and colorectal neoplasia, delayed intervals and active inflammation were associated with an increased AN risk. Conversely, surveillance compliant with primary quality indicators was associated with a reduced AN risk.

Surveillance is widely endorsed in international IBD guidelines, although few studies have assessed the impact of surveillance quality on AN risk.[4,26] Our study showed an AN risk reduction in patients undergoing surveillance compliant with primary quality indicators. This finding is in line with a systematic review and meta-analysis which reports a pooled OR of 0.58 (95% CI, 0.24–0.80) for CRC development in patients who underwent surveillance (vs no surveillance). However, the latter study included historical cohorts, hampered by lack of quality assessment, different endoscopic techniques and adenoma detection methods.[5] More recent studies evaluating surveillance effectiveness reported conflicting results. One study reported a reduced CRC incidence, whereas the other reported a higher AN incidence in patients undergoing surveillance.[27,28] These differences might be the result from different study designs and definitions of surveillance. Importantly, both studies did not primarily assess quality of surveillance. Another study reported low CRC rates in a cohort with high guideline adherence but did not include a reference group for comparison.[29] Our study addressed these limitations and underlines the importance of surveillance procedures compliant with quality indicators to reduce the risk of missed precursor lesions (IND/LGD) and, subsequently, preventable AN.

We observed that delayed surveillance colonoscopies were independently associated with an increased AN risk, underlining the importance of the guidelines' recommended surveillance intervals.[4,26] Moreover, active inflammation during surveillance was associated with AN risk, regardless of severity or extent, as illustrated by the overlapping CIs. Active inflammation is considered the main driver of AN development in IBD but may also reduce mucosal visualization during surveillance, increase the risk of missed precursor lesions of AN, and impair histologic assessment.[8] The association of active inflammation with AN remained significant after adjustment for risk factors for AN, cumulative inflammatory burden, and extensive disease. Adjustment for these factors might not fully resolve residual confounding, but these findings support the dual role for mucosal inflammation both as a risk factor for AN and by reducing the quality of surveillance.[21,23] In line, a recent study showed an increased dysplasia yield of random biopsies in patients with active inflammation and dysplasia compared with controls with dysplasia and inactive disease, likely due to the inability to delineate lesions in inflamed mucosa.[10] Finally, insufficient bowel preparation and lack of cecal intubation showed ORs for AN risk in line with previous studies although statistically not significant, likely due to the low prevalence (4.1%–5.5%).[30,31]

We observed a reduced AN risk if dye-based chromoendoscopy was employed, confirming guideline recommendations for this modality as summarized in a recent

meta-analysis.[11] In line with our findings, the benefits of virtual chromoendoscopy remain under debate.[32,33] Endoscopist expertise has previously been associated with colonoscopy outcomes, including the risk of missed neoplasia in the non-IBD population.[12] By contrast, we found a nonsignificant AN risk reduction if endoscopic surveillance was performed by an IBD specialist compared with residents. To our knowledge, there are no other IBD studies assessing endoscopic surveillance expertise. An academic setting did not significantly impact AN risk, in line with a study showing high-quality colonoscopy performance across different hospital types in the United States.[34]

Current guidelines recommend a shortened (1–3 yearly) surveillance interval in case of extensive disease and active inflammation detected during surveillance.[4] Our results indicate that these shortened intervals may not always be sufficient. This is illustrated by the relatively high rate (n = 22 [16.1%]) of cases with AN on a background of active inflammation at the preceding surveillance colonoscopy, despite adhering to these stricter guideline intervals. Even with the available biological and small molecule therapies, it remains challenging in clinical practice to achieve sufficient disease control in patients with severe IBD phenotypes similar to cases in this study. This underlines the need for more effective pharmacological interventions as well as enhanced endoscopic visualization techniques that may include the future use of artificial intelligence.

Importantly, almost 30% of the patients in our cohort did not undergo any endoscopic surveillance prior to diagnosis of the index lesion, without a significant difference between cases and controls. This might be the result of non-surveillance (diagnostic or therapeutic) colonoscopies performed prior index lesion detection, limiting the risk of missed precursor lesions, as substantiated by our sensitivity analysis. Although the considerable proportion of patients without surveillance might be a consequence of contemporary guideline adherence and patient or physician preferences, these numbers confirm findings from previous studies. In a large cohort study using the U.S. Veterans Association database, only 30% of IBD patients underwent a surveillance colonoscopy within 5 years prior to CRC diagnosis.[7] A recent European cohort study reported that only 27% of patients received a timely first screening colonoscopy with subsequent surveillance according to guideline intervals.[28] Increasing participation of IBD patients in structured endoscopic surveillance programs is a first step toward reducing AN risk.

This study has several strengths. The PALGA search enabled us to create 2 large cohorts of IBD patients from academic and nonacademic hospitals. This is the first

study in IBD primarily investigating the impact of surveillance quality indicators. The similar follow-up duration and number of endoscopic procedures between cases and controls prior to index lesion detection enabled us to calculate a cumulative inflammatory burden score. We used this score as confounder to assess active inflammation during surveillance as quality indicator for mucosal visualization. We used all colonoscopies for calculation, as patients frequently had inconsistently scheduled surveillance, potentially resulting in an underestimation of the inflammatory burden if only surveillance colonoscopies were used. We performed multiple sensitivity analyses to evaluate the robustness of our results.

There are also limitations to discuss, most importantly the retrospective design of this study. Consequently, data are lacking, such as withdrawal time, as this quality indicator is inconsistently reported in endoscopy reports. Although nationwide registries and randomized controlled trials would be beneficial in a definitive assessment of the effectiveness of surveillance without aforementioned limitations, these are not feasible in the foreseeable future due to ethical, time and financial constraints. We selected patients with a surveillance colonoscopy and IND or LGD or AN on subsequent colonoscopy as controls and cases, respectively. This methodological setting allowed for a comparison with patients with intermediate to high risk profiles similar to our cases with AN. This choice of controls may limit extrapolation of our findings to patients who do not develop dysplasia over their lifetime at all, although one could speculate that endoscopic surveillance is of greater clinical relevance for high-risk groups compared with low-risk patients with IBD who may never develop AN. The (virtual) chromoendoscopy rate in this study was low and might reflect local preferences, available expertise, and time-dependent trends.[28,35] Alternatively, one could hypothesize that active inflammation or insufficient bowel preparation resulted in the selection of white light endoscopy rather than chromoendoscopy. Last, patient adherence is an important factor in surveillance,[36] but the exact reasons for absent or delayed surveillance were rarely reported in patient files.

In conclusion, we observed in this multicenter case-control study including patients with IBD and colorectal neoplasia that surveillance compliant with primary quality indicators is associated with AN risk reduction. Active inflammation and delayed colonoscopy intervals are frequently present and limit the effectiveness of surveillance. These findings underline the need for participation in surveillance programs, quality indicator compliance, and focus on achieving endoscopic remission prior to scheduling surveillance colonoscopies.

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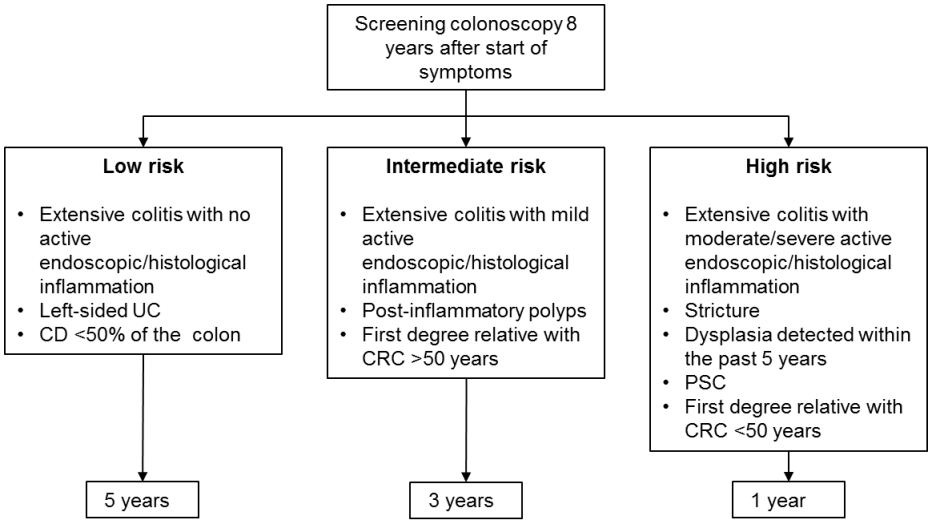
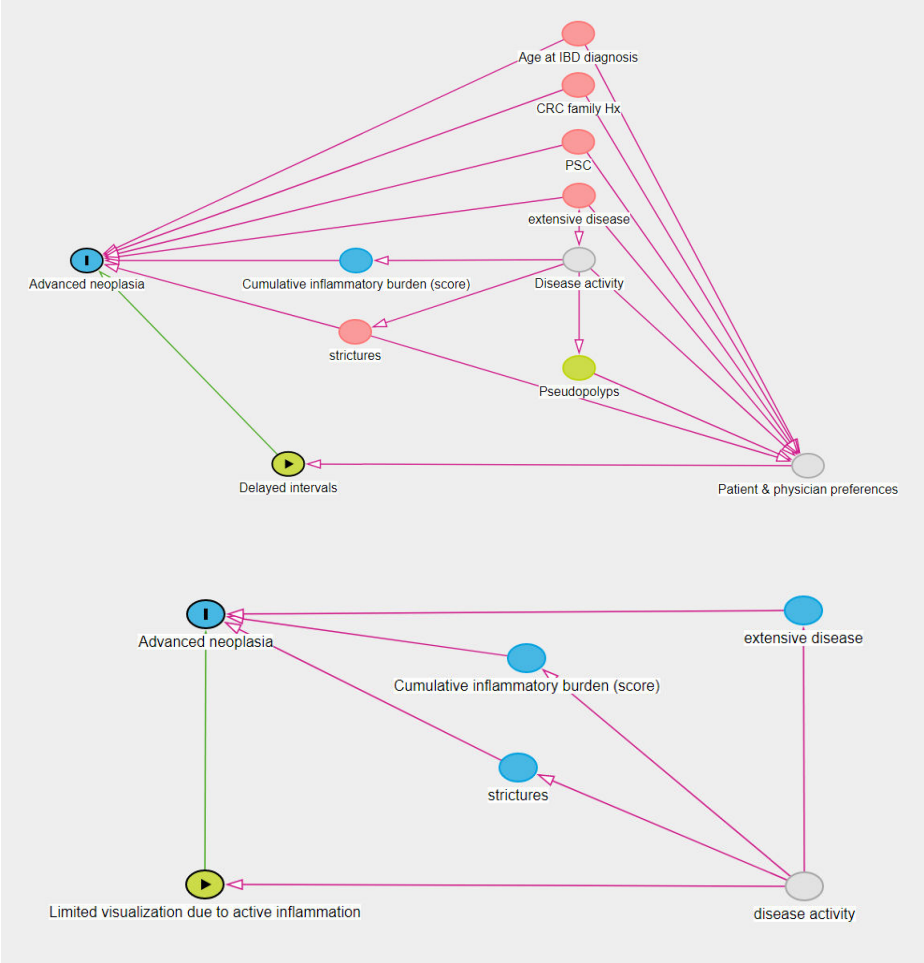
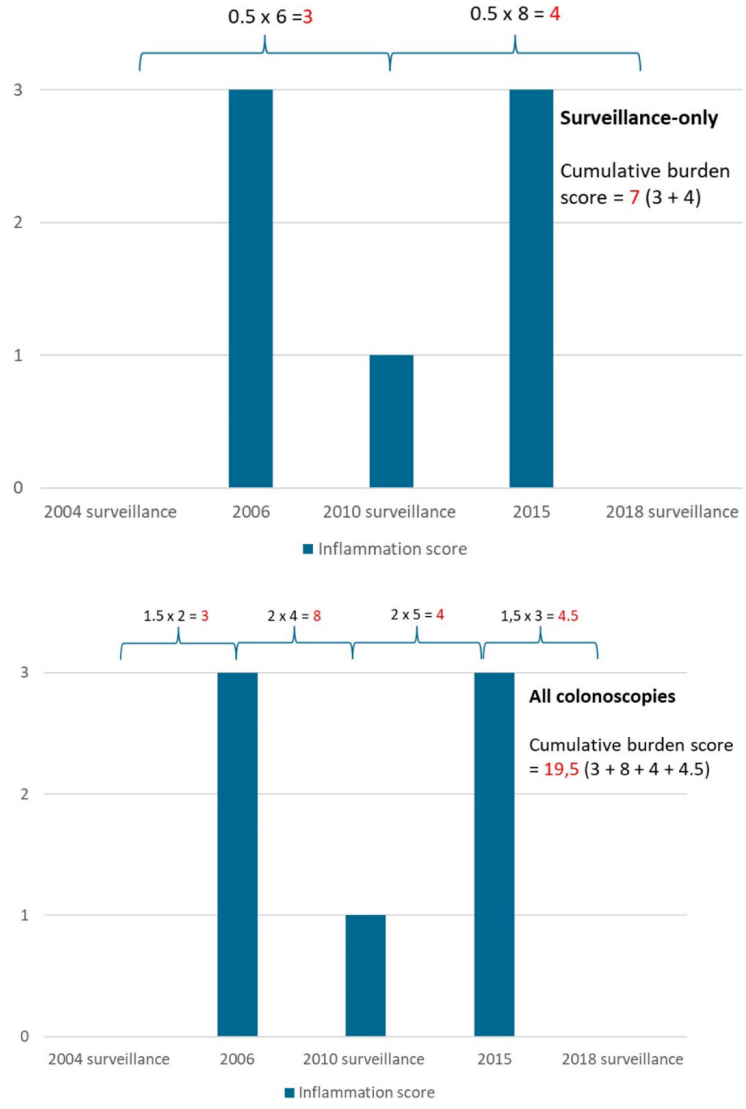
Supplementary Material



Supplementary Figure 1. Overview of the British Society of Gastroenterology surveillance guideline, risk stratification flowchart. CD, Crohn's disease; CRC, colorectal cancer; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.



Supplementary Figure 2. Causal diagrams made in Dagitty for assessment of confounding pathways between quality of surveillance and advanced neoplasia. Gray oval: unobserved/not quantifiable. Red oval: ancestor of exposure and outcome. Green oval: ancestor of exposure. Blue oval: ancestor of outcome. I: primary outcome. Triangle: exposure of interest. Green line: path of interest. Red lines: biasing paths. CRC, colorectal cancer; Hx, history; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis.



Supplementary Figure 3. Example illustrating how the inflammatory burden score was calculated with a patient who had surveillance colonoscopies in 2004, 2010, and 2018 and non-surveillance colonoscopies in 2006 and 2015. The mean endoscopic inflammation severity (0 = absence or inactive inflammation, 1 = mild, 2 = moderate, 3 = severe) between each interval is multiplied with the length of the interval and summed into the cumulative inflammatory burden score. As illustrated, omission of non-surveillance colonoscopies results in an underestimation of the true inflammatory burden.

Supplementary table 1. Index lesion characteristics.

	Cases (AN) (n=137)	Controls (IND/ LGD) (n=138)	Total (n=275)
Neoplasia grade, n [%]			
IND	0 [0.0]	5 [3.6]	5 [1.8]
LGD	0 [0.0]	133 [96.4]	133 [48.4]
HGD	59 [43.1]	0 [0.0]	59 [21.5]
CRC	78 [56.9]	0 [0.0]	78 [28.4]
Morphology, n [%]			
Visible	126 [92.0]	125 [90.6]	251 [91.3]
Not resected	14 [10.2]	5 [3.6]	19 [6.9]
Invisible	11 [8.0]	8 [5.8]	19 [6.9]
Not resected	1 [0.7]	2 [1.4]	3 [1.1]
Unknown	0 [0.0]	5 [3.6]	5 [1.8]

AN, advanced neoplasia; CRC, colorectal cancer; HGD, high-grade dysplasia; IND, indefinite for dysplasia; LGD, low-grade dysplasia.

Supplementary table 2. Absolute frequencies of quality of surveillance prior to index lesion diagnosis, including simultaneous occurrence of reasons for inadequate surveillance.

	Cases (AN) (n=137)	Controls (IND/LGD) (n=138)	Total (n=275)
No surveillance [a], n [%]	38 [27.7]	43 [31.2]	81 [29.5]
Detected at screening colonoscopy, n [%]	1 [0.7]	4 [2.8]	5 [1.8]
High-quality surveillance, n [%]	14 [10.2]	27 [19.6]	41 [14.9]
Non-compliance with quality indicators Presence of, n [%]:			36 [13.1]
Delayed interval	16 [11.7]	20 [14.5]	41 [14.9]
Inflammation	22 [16.1]	19 [13.8]	1 [0.4]
Inadequate BP	0 [0.0]	1 [0.7]	3 [1.1]
Incomplete procedure	0 [0.0]	3 [2.2]	53 [19.3]
Delayed interval + inflammation	38 [27.7]	15 [10.9]	3 [1.1]
Delayed interval + inadequate BP	2 [1.5]	1 [0.7]	2 [0.7]
Delayed interval + incomplete	1 [0.7]	1 [0.7]	4 [1.5]
Inflammation + inadequate BP	1 [0.7]	3 [2.2]	4 [1.5]
Inflammation + incomplete	3 [2.2]	1 [0.7]	1 [0.4]
Inadequate BP + incomplete	1 [0.7]	0 [0.0]	67 [24.4]
Subtotal >1	46 [33.6]	21 [15.2]	148 [53.8]
Subtotal	84 [61.3]	64 [46.4]	

AN, advanced neoplasia; BP, bowel preparation; IND, indefinite for dysplasia; LGD, low-grade dysplasia.
[a] All with non-surveillance endoscopies prior to the index lesion detection (colonoscopy: n=18 [22.2%]; sigmoidoscopy: n=63 [77.8%])

Supplementary table 3. Secondary quality indicators for the surveillance colonoscopy prior to index lesion detection.

	Cases (AN)	Controls (IND/LGD)	Total
Dye-based chromo-endoscopy, n (%)	1/98 (1.0)	8/91 (8.8)	9/189 (4.8)
Virtual chromo-endoscopy, n (%)	4/79 (5.1)	4/66 (6.1)	8/145 (5.5)[a]
Setting, n (%)	77/98 (78.6)	77/91 (84.6)	154/189 (81.5)
Academic hospital Community hospital	21/98 (21.4)	14/91 (15.4)	35/189 (18.5)
Endoscopist expertise[1], n (%)			
IBD-specialist	23/78 (29.5)	30/79 (38.0)	53/157 (33.8)[b]
Gastroenterologist without IBD-specialty	25/78 (32.1)	22/79 (27.8)	47/157 (29.9)[b]
Supervised Resident	30/78 (38.5)	27/79 (34.2)	57/157 (36.3)[b]
Biopsy strategy, n (%)			
Only random biopsies	21/77 (27.3)	29/79 (36.7)	50/156 (32.1)[c]
Only targeted biopsies	19/77 (24.7)	11/79 (13.9)	30/156 (19.2)[c]
Both random and targeted biopsies	31/77 (40.3)	30/79 (38.0)	61/156 (39.1)[c]
No biopsies	6/77 (7.8)	9/79 (11.4)	15/156 (9.6)[c]
Number of random biopsies, median (IQR)	20.5 (9.8-27.0)	22.0 (11.0-28.0)	22.0 (10.0-27.5)[c]

AN, advanced neoplasia; CD, Crohn's disease; IBD, inflammatory bowel disease; IND, indefinite for dysplasia; LGD, low-grade dysplasia.

[a] 44 missing values

[b] 32 missing values

[c] 33 missing values

Chapter 3

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

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Submitted

Abstract

Background and aims

The diagnosis of inflammatory bowel disease (IBD) associated 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 to 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.

Keywords: recurrence, treatment, Crohn

Introduction

Inflammatory bowel disease (IBD) patients bear an increased colorectal cancer (CRC) risk and undergo regular endoscopic surveillance to detect and remove pre-malignant 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 (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 to 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 inter-observer 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 quality of biopsy sampling and the presence of severe [12,13]. Current guidelines suggest consultation of a second gastrointestinal 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 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 Izv2019-87) 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 BSG 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', '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 December 1, 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 (IBD-U), and (2) a histological diagnosis of HGD. Patients were excluded in case of (1) advanced neoplasia 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) advanced neoplasia.

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 IND, LGD or advanced neoplasia during follow-up after treatment of HGD.

Revision and dedicated GI 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 (SV, IN) 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. as absence of dysplasia, IND, LGD, HGD or CRC [12]. 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: SV, IN) 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, non-polypoid visible or invisible, the latter detected with random biopsies[20]), and endoscopic 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 in five-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 [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 (IR) and cumulative incidences were displayed with 95% confidence intervals (CI). 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, NY, 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 (figure 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 is shown in figure 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%)).

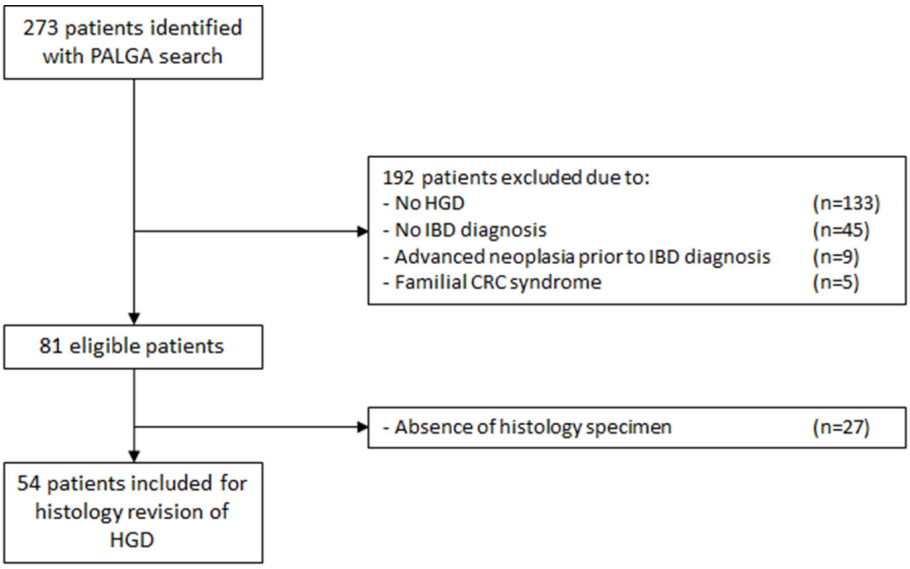

Figure 1. Patient selection flowchart.
HGD: high-grade dysplasia, CRC: colorectal cancer.

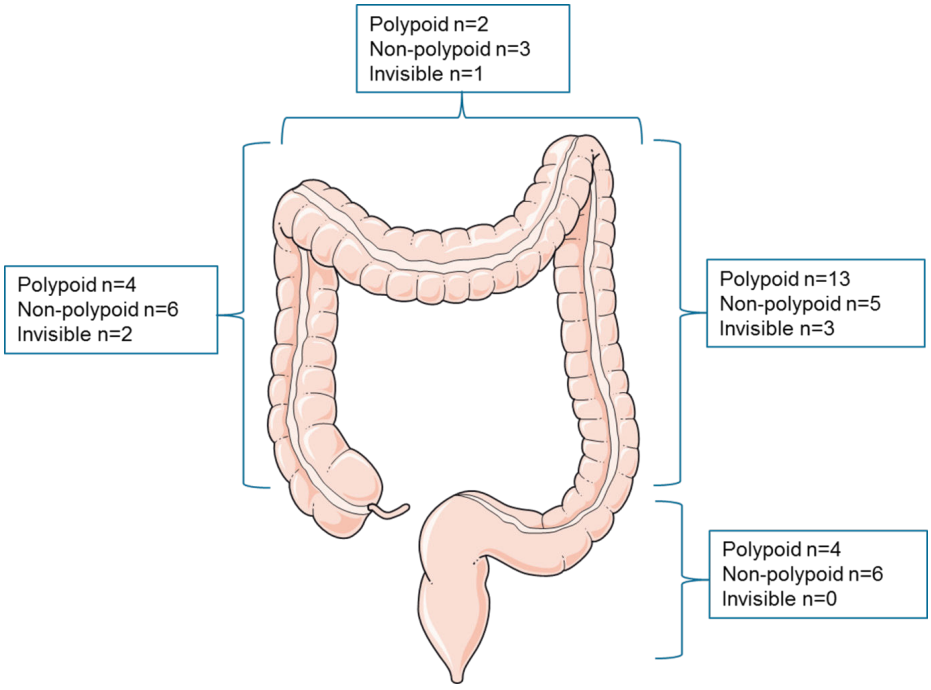

Figure 2. HGD Localization and morphology* [24].
* n=5 patients with multifocal lesions in different colonic segments not included.

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#, n [%]					
Polypoid	26 [49.1]	15 [83.3]	10 [34.5]	1 [16.7]	**<0.01**
Non-polypoid	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]	2 [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	26 [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]	

Table 1. Continued

Characteristics	Before revision and consensus	After revision and consensus			
	HGD (n=54)	IND/LGD (n=18)	HGD (n=30)	CRC (n=6)	P value
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[##], 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
Post-inflammatory 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. IQR: interquartile range. IND: indefinite for dysplasia. LGD: low-grade dysplasia. HGD: high-grade dysplasia. CRC: colorectal cancer. # 2 missings. ## 6 missings

Dedicated GI 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). Inter-observer disagreement between the two pathologists was reported in 18 (32.7%) patients between HGD and LGD, in 3 (5.6%) between HGD and CRC and in one (1.8%) between IND and absence of dysplasia. This resulted in a fair inter-observer 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, 17 (31.5%) lesions were downgraded to LGD, one (1.9%) to IND and 6 (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). Examples of LGD, HGD and CRC after revision and dedicated GI pathologist consensus are displayed in supplementary figure 1.

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*, n [%]	3 [5.6]	1 [5.6]	1 [3.3]	1 [16.7]

IND: indefinite for dysplasia. LGD: low-grade dysplasia. HGD: high-grade dysplasia. CRC: colorectal cancer.
*13 missings.

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 four 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).

Synchronous CRC

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 non-polypoid HGD (n=6 (85.7%) vs n=14 (30.4%), p=0.01, supplementary table 3). 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 advanced neoplasia, p=0.04). Synchronous CRC was diagnosed median eight 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 advanced neoplasia was 23 months (IQR 8.5-85.5 months, figure 3 and supplementary figure 2A-B). 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 (figure 3).

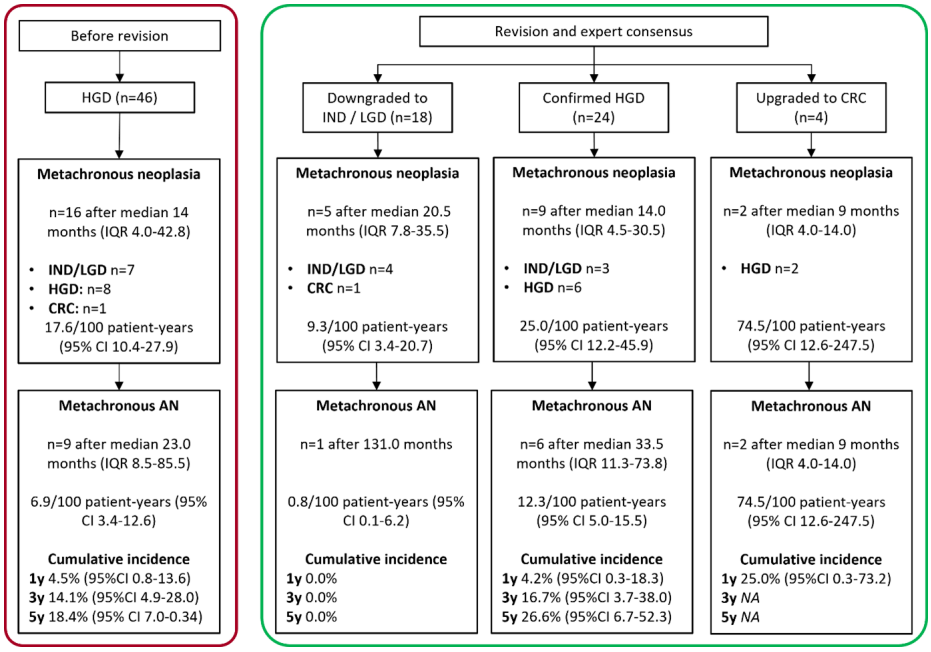

Figure 3. Overview of (cumulative) metachronous neoplasia incidence after revision with dedicated GI pathologist consensus, excluding synchronous CRC (n=7).

AN: advanced neoplasia. CI: confidence interval. HGD: high-grade dysplasia. IND: indefinite for dysplasia. LGD: low-grade dysplasia. CRC: colorectal cancer. y: year. PY: patient-years NA: not available.

Patients with a downgraded lesion showed a lower cumulative incidence of metachronous advanced neoplasia compared to 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), figure 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 advanced neoplasia during follow-up) was not significantly different between downgraded lesions and confirmed advanced neoplasia (Gray's test p=0.30, figure 4B). Cumulative incidence functions including competing event curves are displayed in supplementary figure 3A-B.

Sensitivity analysis

The cumulative incidence of metachronous advanced neoplasia did not differ between patients without histopathological HGD specimen available (and therefore excluded from main analyses (n=27), figure 1) and those with specimens available ((n=54), p=0.42).

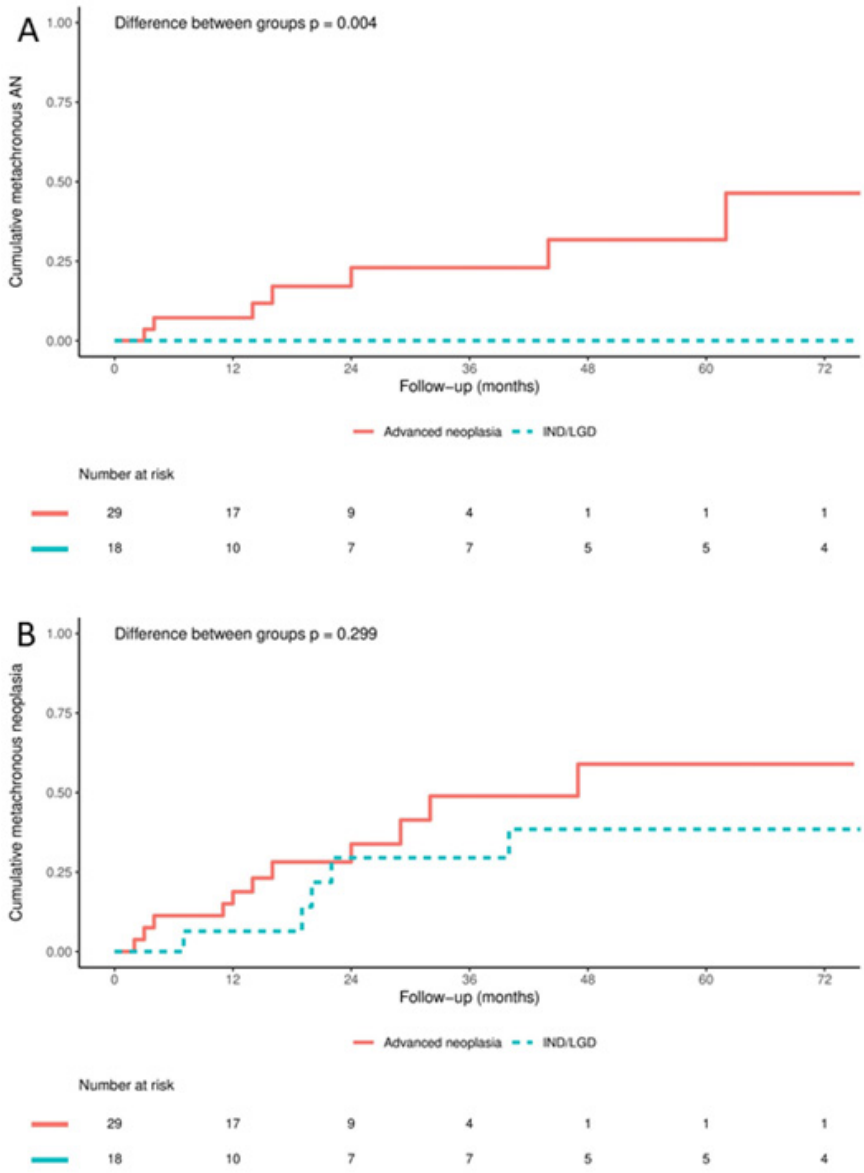

Figure 4A-B. Cumulative incidence function for (A) metachronous advanced neoplasia (B) and metachronous neoplasia (any type: IND/LGD or advanced neoplasia), after revision and expert pathologist consensus.

IND: indefinite for dysplasia; LGD: low-grade dysplasia.

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 advanced neoplasia 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 advanced neoplasia 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 an dedicated GI pathologist consensus meeting could be an effective intervention for cases with disagreement between pathologists, underlined by the significantly lower cumulative incidence of metachronous advanced neoplasia in patients with revised IND/LGD in this study.

The clinical consequences of HGD are significant, with a five-year cumulative incidence of metachronous advanced neoplasia of 26.6%. HGD can be considered a tipping point between endoscopic treatment and colectomy. An accurate diagnosis is therefore essential for 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 upgrade to CRC after consensus initially underwent an endoscopic resection, thus in retrospect deviating from guidelines' recommendations.

Importantly, even after accurate diagnosis of HGD, the metachronous advanced neoplasia and synchronous CRC rates are high. Compared to LGD, HGD harbors an almost three-times higher 5-year cumulative incidence of metachronous advanced neoplasia (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 1984-2013 [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 non-academic 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 non-polypoid (flat or invisible) with higher recurrence rates compared to sporadic neoplasia. Only 50 percent 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 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 an dedicated GI panel, similar to other studies on 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 was downgraded, corresponding with a lower cumulative incidence of metachronous advanced neoplasia. In retrospect, this may have resulted in overtreatment by colectomy

for this group. Synchronous and metachronous advanced neoplasia frequently occurred, underlining the importance of strict surveillance adherence following a confirmed diagnosis of HGD.

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Supplementary files

Supplementary table 1. Outcomes of revision per individual pathologist

Revised diagnosis	Pathologist 1	Pathologist 2
No neoplasia, n[%]	0 [0.0]	1 [1.9]
IND, n[%]	1.0 [1.9]	0 [0.0]
LGD, n[%]	14 [25.9]	30 [55.6]
HGD, n[%]	36 [66.7]	17 [31.5]
CRC, n[%]	3 [5.6]	6 [11.1]

Supplementary table 2. Time-frame of lesion diagnosis.

	After revision and consensus (n=54)			
Year of diagnosis	**IND/LGD (n=18)**	**HGD (n=30)**	**CRC (n=6)**	**Total (n=54)**
<2005, n [%]	0 [0.0]	1 [100.0]	[0.0]	1 [100.0]
2005-2009, n [%]	8 [61.5]	5 [38.5]	0 [0.0]	13 [100.0]
2010-2014, n [%]	9 [37.5]	13 [54.2]	2 [3.7]	24 [100.0]
2015>, n [%]	1 [6.3]	11 [68.8]	4 [25.0]	16 [100.0]

IND: indefinite for dysplasia, LGD: low-grade dysplasia, HGD: high-grade dysplasia, CRC: colorectal cancer

Supplementary table 3. Characteristics of patients with synchronous CRC

Characteristics	Synchronous CRC (n=7)	Without synchronous CRC (n=47)	p-value
Male sex, n [%]	4 [57.1]	30 [63.8]	0.73
Disease type, n [%]			
Ulcerative colitis	4 [57.1]	29 [61.7]	0.80
Crohn's disease	3 [42.9]	16 [34.0]	
IBD-undetermined	0 [0.0]	2 [4.3]	
Age at IBD diagnosis in years, median [IQR]	19.0 [16.0-40.0]	36.0 [22.0-45.0]	0.16
Time until lesion in years, median [IQR]	19.0 [12.0-24.0]	18.0 [11.0-31.0]	0.98
Lesion morphology#, n [%]			
Polypoid	0 [0.0]	26 [56.5]	**0.01**
Non-polypoid	6 [85.7]	14 [30.4]	
Invisible	1 [14.3]	6 [13.0]	
Multifocal lesion, n [%]	1 [14.3]	18 [38.3]	0.22
Maximal endoscopic disease extent (Montreal), n [%]			0.50
E1	0 [0.0]	3 [6.4]	
E2	0 [0.0]	4 [8.5]	
E3	4 [57.1]	26 [55.3]	
<50% (Crohn's disease)	0 [0.0]	5 [10.6]	
>50% (Crohn's disease)	3 [42.9]	9 [19.1]	
Maximal histological disease extent (Montreal), n [%]			
E1	0 [0.0]	9 [19.1]	0.32
E2	0 [0.0]	4 [8.5]	
E3	4 [57.1]	22 [46.8]	
<50% (Crohn's disease)	0 [0.0]	4 [8.5]	
>50% (Crohn's disease)	3 [42.9]	8 [17.0]	
For Crohn's disease: disease behavior (Montreal), n [%]			
B1	1 [33.3]	3 [18.8]	0.69
B2	1 [33.3]	5 [31.3]	
B3	1 [33.3]	3 [18.8]	
B2+3	0 [0.0]	5 [31.3]	
P	1 [14.3]	6 [12.8]	
Medication exposure, n [%]			
5-aminosalicylates	4 [57.1]	26 [59.1]	0.92
Immunomodulators	2 [28.6]	17 [31.5]	0.69
Biologicals/small molecules/ciclosporin	2 [28.6]	14 [31.8]	0.86
BSG guideline colorectal cancer risk stratification[31], n [%]			
No indication	0 [0.0]	8 [17.0]	0.63
Low	1 [14.3]	4 [8.5]	
Intermediate	3 [42.9]	14 [29.8]	
High	3 [42.9]	21 [44.7]	

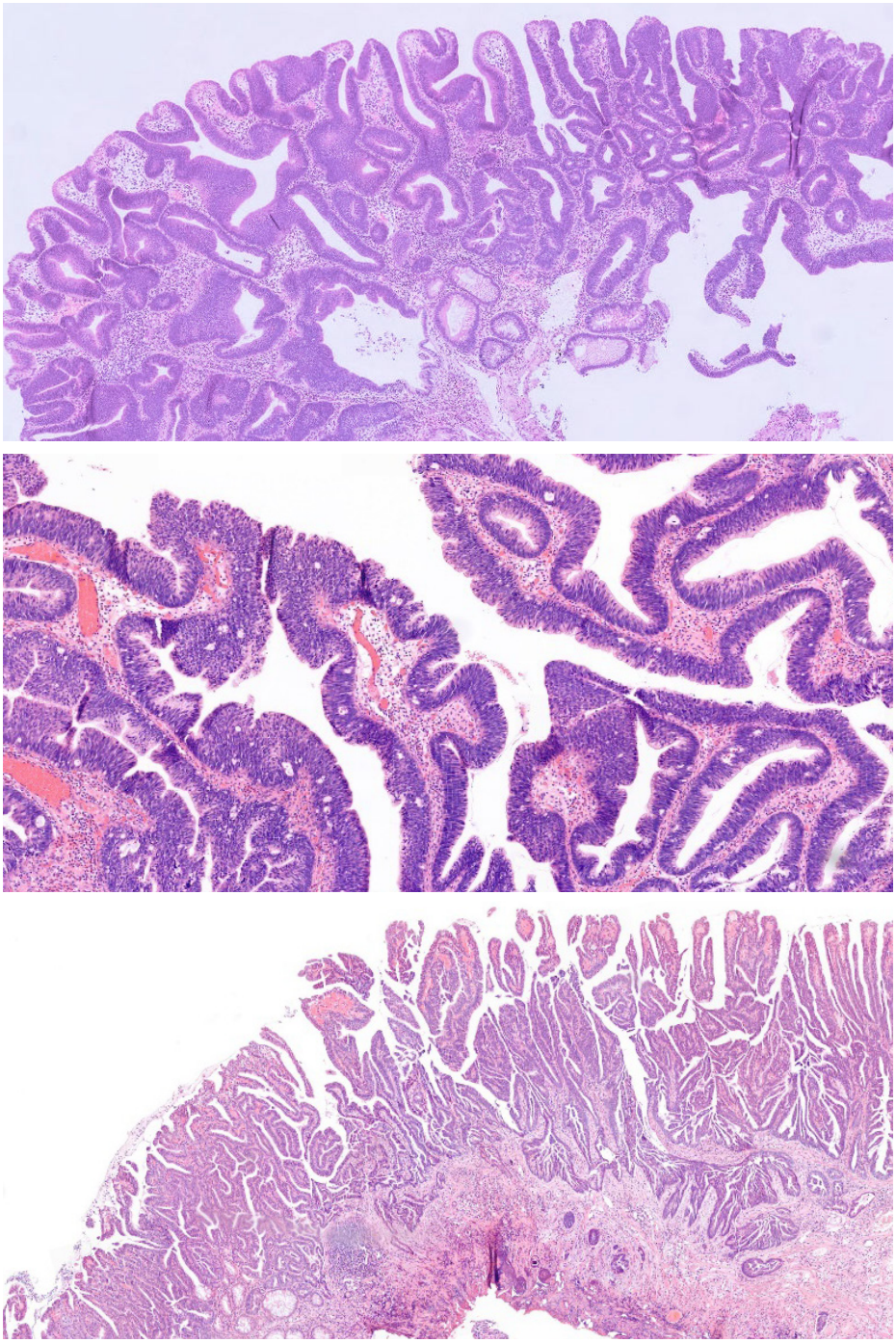
Supplementary table 3. Continued

Characteristics	Synchronous CRC (n=7)	Without synchronous CRC (n=47)	p-value
For ulcerative colitis/IBD-undetermined: stricture, n [%]	2 [40.0]	4 [12.9]	0.13
Family history of colorectal cancer, n [%]	2 [28.6]	5 [10.6]	0.30
Smoking[##], n [%]			
Current	1 [14.3]	2 [4.3]	0.51
Past	2 [28.6]	9 [19.1]	
Never	4 [57.1]	30 [63.8]	
Primary sclerosing cholangitis, n [%]	1 [14.3]	11 [23.4]	0.59
Post-inflammatory polyps, n [%]	2 [28.6]	17 [36.2]	0.69
Prior dysplasia (IND/LGD), n [%]	2 [28.6]	21 [44.7]	0.42
Academic center, n [%]	7 [100.0]	40 [85.1]	0.27

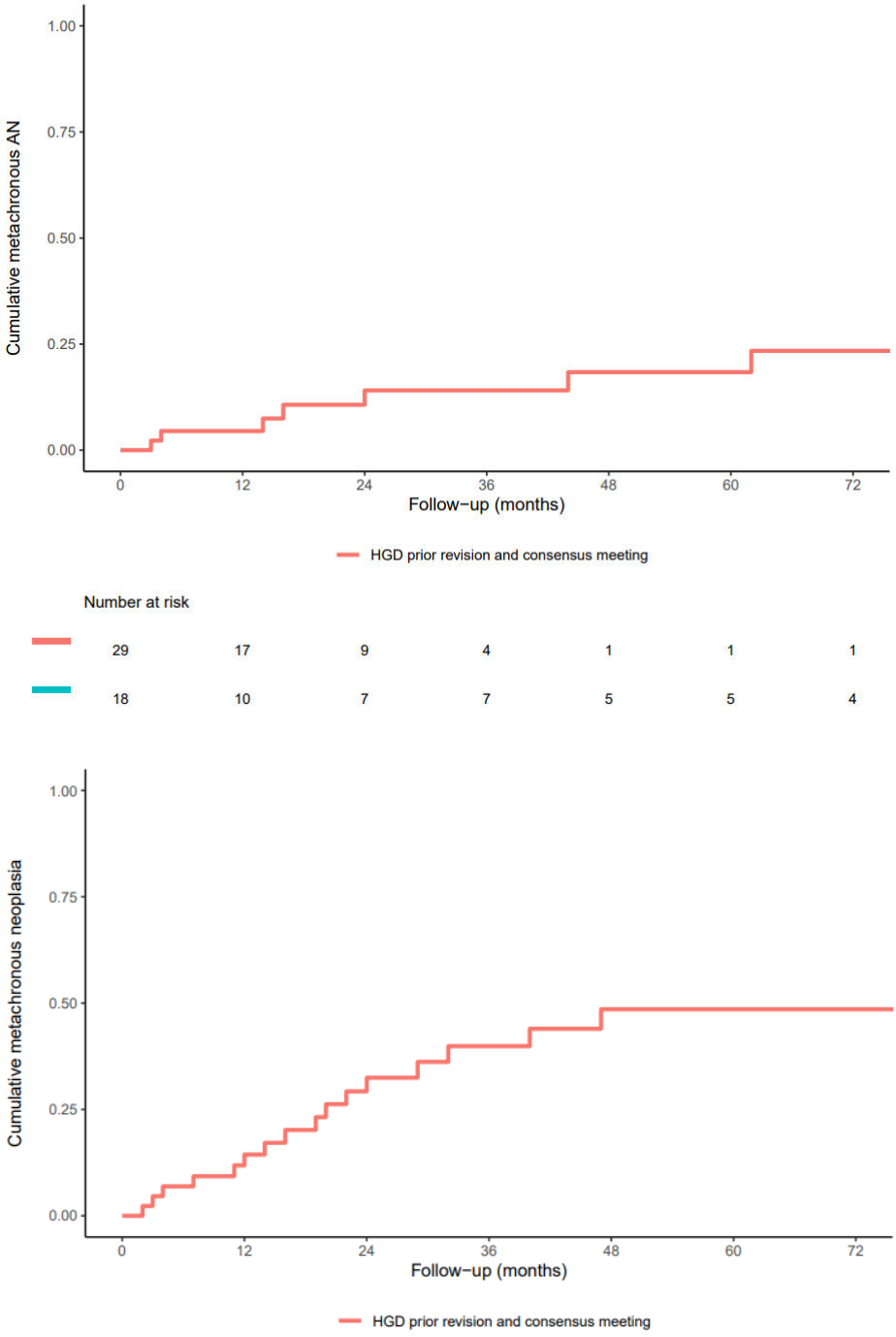
BSG: British Society of Gastroenterology. IQR: interquartile range. IND: indefinite for dysplasia. LGD: low-grade dysplasia. HGD: high-grade dysplasia. CRC: colorectal cancer.

[#] 2 missings.

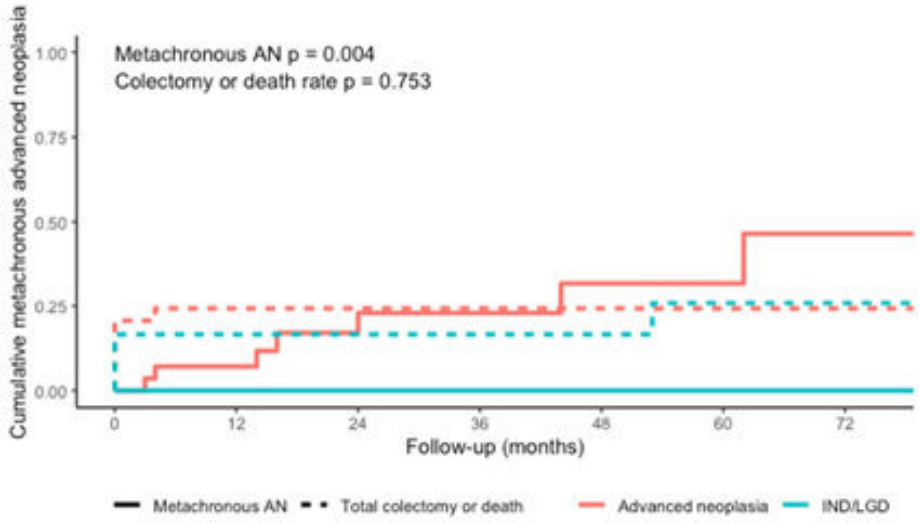
[##] 6 missings

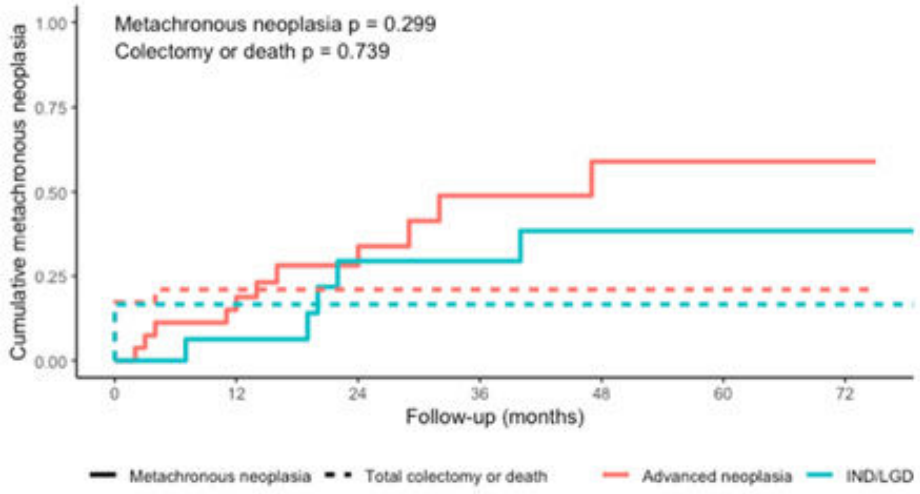


Supplementary figure 1. Examples of (upper) LGD (middle) HGD and (lower) CRC after revision and expert pathologist consensus.



Supplementary figure 2A-B. Cumulative incidence functions for (A) metachronous advanced neoplasia and for (B) any type of neoplasia of HGD before revision and expert pathologist consensus.





Supplementary figure 3A-B. Cumulative incidence functions for metachronous advanced neoplasia and for any type of neoplasia in confirmed IND/LGD and advanced neoplasia, including incidence curves for competing events*.

IND: indefinite for dysplasia; LGD: low-grade dysplasia.

*After treatment, one (2.1%) patient received a total colectomy after 53 months due to metachronous, recurring dysplasia (LGD) and another patients died of head trauma after 4 months. Both were considered competing events

Part II

Treatment and follow-up

Chapter 4

Endoscopic and surgical treatment outcomes of colitis-associated advanced neoplasia: a multicenter cohort study

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on behalf of the Dutch Initiative on Crohn's and Colitis (ICC) and the Dutch Nationwide Pathology Databank (PALGA) group

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Abstract

Background

Inflammatory bowel disease (IBD) patients are at increased risk of advanced neoplasia (high-grade dysplasia (HGD) or colorectal cancer (CRC)). We aimed to (1) assess synchronous and metachronous neoplasia following (sub)total or proctocolectomy, partial colectomy or endoscopic resection for advanced neoplasia in IBD and (2) identify factors associated with treatment choice.

Material and methods

In this retrospective multicenter cohort study, we used the Dutch nationwide pathology databank (PALGA) to identify patients diagnosed with IBD and colonic AN between 1991 and 2020 in seven hospitals in the Netherlands. Logistic and Fine&Gray's subdistribution hazard models were used to assess adjusted subdistribution hazard ratios (asHR) for metachronous neoplasia and associations with treatment choice.

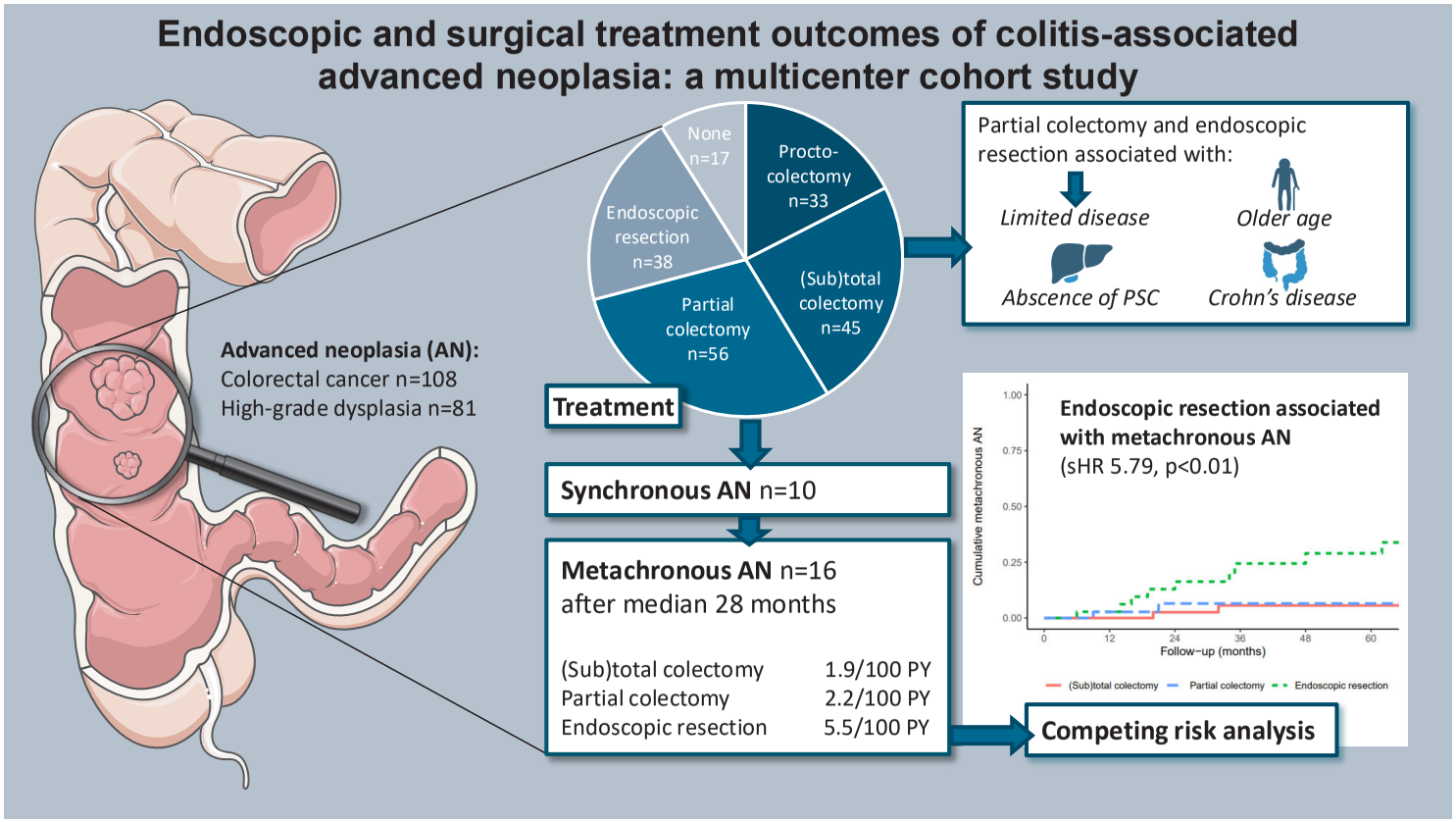
Results

We included 189 patients (HGD n=81; CRC n=108). Patients were treated with proctocolectomy (n=33), (sub)total colectomy (n=45), partial colectomy (n=56) and endoscopic resection (n=38). Partial colectomy was more frequently performed in patients with limited disease and older age, with similar patient characteristics between Crohn's disease and ulcerative colitis. Synchronous neoplasia was found in 43 patients (25.0%; (sub)total or proctocolectomy n=22, partial colectomy n=8, endoscopic resection n=13). We found a metachronous neoplasia rate of 6.1, 11.5 and 13.7 per 100 patient-years after (sub)total colectomy, partial colectomy and endoscopic resection, respectively. Endoscopic resection, but not partial colectomy, was associated with an increased metachronous neoplasia risk (asHR 4.16, 95% CI 1.64-10.54, $p<0.01$) compared to (sub)total colectomy.

Conclusion

After confounder adjustment, partial colectomy yielded a similar metachronous neoplasia risk compared to (sub)total colectomy. High metachronous neoplasia rates after endoscopic resection underline the importance of strict subsequent endoscopic surveillance.

Keywords: Inflammatory bowel disease; dysplasia; colorectal cancer; colectomy; endoscopic resection


Endoscopic and surgical treatment outcomes of colitis-associated advanced neoplasia: a multicenter cohort study
Advanced neoplasia (AN):
Colorectal cancer n=108
High-grade dysplasia n=81
None n=17
Procto-colectomy n=33
Endoscopic resection n=38
(Sub)total colectomy n=45
Partial colectomy n=56
Treatment
Partial colectomy and endoscopic resection associated with:
Limited disease
Older age
Abscence of PSC
Crohn's disease
Synchronous AN n=10
Metachronous AN n=16
after median 28 months
(Sub)total colectomy 1.9/100 PY
Partial colectomy 2.2/100 PY
Endoscopic resection 5.5/100 PY
Endoscopic resection associated with metachronous AN
(sHR 5.79, p<0.01)
Cumulative metachronous AN
1.00
0.75
0.50
0.25
0.00
0
12
24
36
48
60
Follow−up (months)
(Sub)total colectomy
Partial colectomy
Endoscopic resection
Competing risk analysis

Introduction

Inflammatory bowel disease (IBD) patients have a 1.4 to 1.7-fold increased risk of developing colorectal cancer (CRC) compared to the general population [1,2]. Endoscopic surveillance is recommended to detect and remove colorectal neoplasia, including indefinite for dysplasia, low-grade dysplasia, high-grade dysplasia (HGD) and CRC. In case advanced neoplasia (including HGD and CRC) is detected, complete lesion resection is recommended to prevent residual and recurring colorectal neoplasia.

Historically, a proctocolectomy or (sub)total colectomy was recommended for colorectal advanced neoplasia due to the high risk of synchronous and metachronous (non-visible) colorectal advanced neoplasia [3-6]. This surgical approach potentially results in a permanent ileostomy or ileal pouch-anal anastomosis, significantly impacting quality of life [7]. However, advances in surveillance techniques such as high-definition and chromo-endoscopy have improved lesion detection, limiting the risk of missed synchronous neoplasia [8,9]. A recent study in Crohn's disease (CD) patients with CRC reported no increased metachronous CRC risk after partial colectomy compared to (sub)total or proctocolectomy, suggesting that a more restrictive surgical approach may be feasible in patients with limited disease [10]. Another study in ulcerative colitis (UC) patients with CRC showed no metachronous CRC after seven years of follow-up, suggesting that partial colectomy might be feasible in elderly patients [11].

An even more colon-sparing approach for advanced neoplasia is endoscopic resection, which could be considered for unifocal dysplastic lesions that appear endoscopically resectable (visible lesions with clear borders that lift well), or when the risk of surgery outweighs potential oncological benefits [12-14]. For CRC, limited data from case series show the feasibility of endoscopic resection in case of early-stage CRC, in line with studies on early CRC in the non-IBD population [15-17]. In addition, there are limited data on factors associated with treatment choice in clinical practice. International guidelines advocate a tailored treatment strategy for advanced neoplasia, in which (sub)total or proctocolectomy remains the current standard, but endoscopic resection and partial colectomy can be considered in a subgroup of patients. However, these recommendations are based on low-quality evidence [12,13].

In this study, we aimed to (1) compare cumulative incidences of synchronous and metachronous colorectal neoplasia as well as mortality following advanced neoplasia in CD and UC patients who underwent proctocolectomy, (sub)total

colectomy, partial colectomy or endoscopic resection, and (2) to determine factors associated with advanced neoplasia treatment choice.

Methods

Design and outcomes

We performed a multicenter retrospective cohort study in seven hospitals in the Netherlands and assessed the following outcomes after proctocolectomy, (sub)total colectomy, partial colectomy and endoscopic resection for advanced neoplasia in CD and UC:

1. Synchronous colorectal neoplasia, defined as co-existence of two or more neoplastic colorectal lesions detected in the initial resection specimen or up to 6 months after treatment of the index lesion, categorized in (a) any neoplasia (independent of grade) and (b) advanced neoplasia (HGD or CRC). [18]
2. Metachronous neoplasia, defined as colorectal neoplasia detected $\geq$6 months after treatment of index advanced neoplasia, categorized in (a) any neoplasia (independent of grade) and (b) only advanced neoplasia, including the impact of IBD type. [19]
3. All-cause mortality
4. Clinical and disease characteristics associated with advanced neoplasia treatment choice.

Patients

The Dutch nationwide pathology databank (PALGA) was searched up to December 1, 2020, to identify patients with IBD and advanced neoplasia in five academic and two peripheral hospitals in the Netherlands. All seven selected centers are high volume IBD centers with accessible electronic patient charts. PALGA has a complete nationwide coverage since 1991. Each report links with an identifier to individual patient records. The search was performed using the following terms: 'ulcerative colitis', 'Crohn's disease', 'indeterminate colitis' and 'chronic idiopathic inflammatory bowel disease' and 'high-grade dysplasia', 'carcinoma in situ' and 'colorectal cancer'. All patients with IBD (UC, CD or IBD-unclassified (IBD-U)) with a histological diagnosis of colorectal advanced neoplasia and available treatment data were included. Exclusion criteria were familial CRC syndrome, advanced neoplasia prior to IBD diagnosis.

Data Collection

We extracted the following data from electronic patient records: Sex, age, IBD type and extent (Limited disease: Montreal classification E1 and E2 (UC) [20], or less than 50% colonic involvement (CD); Extensive disease: Montreal classification E3 (UC), or more than 50% colonic involvement (CD))), IBD duration, CRC family history, smoking, primary sclerosing cholangitis (PSC), post-inflammatory polyps, and CRC risk stratification according to the BSG guideline [21].

In addition, data regarding colorectal neoplasia were collected, including date, grade (indefinite for dysplasia, low-grade dysplasia, HGD or CRC), type (polypoid, non-polypoid, invisible [13]) and location. Index advanced neoplasia was defined as the first colorectal lesion with HGD or CRC. In case of co-existence of two or more advanced lesions, we scored the highest grade. Only for CRC, TNM stage [22] and all-cause mortality were derived using the national cancer registry of the Netherlands (NCR), with nationwide coverage since 1989 [23].

The treatment modality of index advanced neoplasia was collected and categorized as (1) endoscopic resection (snare polypectomy, endoscopic mucosal resection (EMR) or endoscopic submucosal resection (ESD)), (2) partial colectomy (ileocecal resection, segmental resection, right or left hemicolectomy) or (3) (sub)total or proctocolectomy. Endoscopic and surgical follow-up was recorded until the most recent available procedure.

Statistical analysis

Categorical and continuous variables were reported as proportions with percentages and medians with interquartile range (IQR), respectively. Categorical variables were compared with chi-square or Fisher exact tests (for groups with $n \leq 5$) and continuous variables with Mann-Whitney U tests. We performed competing risk analyses with Fine & Gray's subdistribution hazard model to assess metachronous neoplasia, using subdistribution hazard ratios (sHR) with a 95% confidence interval (CI). Death and proctocolectomy were considered competing events. We censored patients at the end of follow-up if no event (metachronous neoplasia, death, or proctocolectomy) occurred. The cumulative metachronous neoplasia and mortality incidence were displayed with cumulative incidence functions. Incidence curves were compared using Gray's test. Considering the long inclusion period of our study and the fact that endoscopic surveillance an treatment techniques have advanced over time, we performed a time-frame analysis excluding all patients with an index lesion <2010. The cut-off point was set on 2010 because of the implementation of high definition devices around this time, and the publication of the first studies on EMR and ESD in

IBD in 2007 and 2008, making endoscopic resection a more widely accepted modality in the subsequent years [24,25]. Associations with treatment modalities were assessed with a multinomial logistic regression model and presented as (adjusted) odds ratios ((a)OR) with 95% CI. Confounder selection for multivariable models was based on clinical relevance and univariable p<0.02. The inflammatory pattern (continuous vs segmental) of UC/IBD-U vs CD could potentially result in different effectiveness of partial and (sub)total) colectomy between IBD types. Therefore, we explored the modifying effect of IBD type on the metachronous (advanced) neoplasia risk. Statistical analyses were performed with SPSS v25 (Armonk, NY, USA) and R v3.6.3 (package "*cmprsk*").

Ethical considerations

This study was approved by the institutional review board of the Radboud University Medical Center (2017-3219) and the scientific committee of PALGA (lzv-2019-87). Our work has been reported in line with the STROCSS criteria and was registered in clinicaltrials.gov (NCT05674773) [26].

Results

Patients

We included 189 IBD patients with advanced neoplasia (supplementary figure 1), including 81 patients with HGD and 108 patients with CRC as index AN, of whom 172 underwent treatment. Of these, 110 (58.2%) were male, 1119 (63.0%) had UC, 23 (12.2%) had PSC, and 136 (72.0%) had extensive disease. Median IBD duration at time of index AN was 19 years (IQR 10.5-25.0) (table 1 and supplementary table 1).

Table 1. Baseline characteristics of n=189 advanced neoplasia patients

Characteristics	(Sub)total and procto colectomy, n= 78	Partial colectomy, n=56	Endoscopic resection, n=38	Total sample[1] (n=189)
Male sex, n [%]	47 [60.3]	32 [57.1]	21 [55.3]	110 [58.2]
Disease, n [%]				
Ulcerative colitis	54 [68.4]	28 [50.9]	25 [65.8]	119 [63.0]
Crohn's disease	23 [29.1]	25 [45.5]	12 [31.6]	65 [34.4]
IBD-unclassified	2 [2.5]	2 [3.6]	1 [2.6]	5 [2.6]
Age at time of IBD diagnosis, median [IQR]	28 [19.0-40.0]	34 [24.0-52.5]	37 [24.0-48.0]	31 [22.0-44.5]
Family history of colorectal cancer, n [%]	8 [14.5]	8 [20.0]	6 [21.4]	22 [11.6]
Smoking, n [%]				
Current	2 [2.5]	3 [5.5]	4 [10.5]	10 [5.3]
Past	10 [12.7]	17 [30.9]	13 [34.2]	42 [22.2]
None	51 [64.6]	25 [45.5]	17 [44.7]	102 [54.0]
PSC, n [%]	17 [21.5]	1 [1.8]	3 [7.9]	23 [12.2]
Post inflammatory polyps, n [%]	35 [44.3]	24 [43.6]	16 [42.1]	86 [45.5]
Maximal endoscopic extent (Montreal), n [%]				
E1 (Ulcerative colitis)	0 [0.0]	2 [6.7]	0 [0.0]	2 [1.0]
E2 (Ulcerative colitis)	7 [12.5]	13 [43.3]	5 [19.2]	26 [13.8]
E3 (Ulcerative colitis)	49 [87.5]	15 [50.0]	21 [80.8]	96 [50.8]
L1 (Crohn's disease)	0 [0.0]	0 [0.0]	3 [25.0]	3 [1.6]
Colon <50% (Crohn's disease)	3 [13.6]	12 [46.2]	5 [41.7]	22 [11.6]
Colon >50% (Crohn's disease)	19 [86.4]	14 [53.8]	4 [33.3]	40 [21.2]
CRC risk classification[2], n [%]				
Low risk	3 [3.8]	12 [21.8]	10 [26.3]	32 [16.9]
Intermediate risk	47 [59.5]	28 [50.9]	18 [47.4]	76 [40.2]
High risk	25 [31.6]	7 [12.7]	6 [15.8]	55 [29.1]
No indication for surveillance	4 [5.1]	8 [14.5]	4 [10.5]	26 [13.8]
Index AN, n [%]				
High-grade dysplasia	33 [42.3]	12 [21.4]	35 [92.1]	81 [42.9]
Colorectal cancer	45 [57.7]	44 [78.6]	3 [7.9]	108 [57.1]
Lesion characteristics, n [%]				
Polypoid	16 [23.2]	16 [39.0]	27 [71.1]	60 [31.7]
Nonpolypoid	46 [66.7]	21 [51.2]	11 [28.9]	83 [43.9]
Invisible	7 [10.1]	4 [9.8]	0 [0.0]	11 [5.8]

Table 1. Continued

Characteristics	(Sub)total and procto colectomy, n= 78	Partial colectomy, n=56	Endoscopic resection, n=38	Total sample[1] (n=189)
Tumor stage[3], n [%]				
I	8 [17.8]	6 [13.6]	3 [100.0]	19 [17.6]
II	15 [33.3]	17 [38.6]	0 [0.0]	34 [31.5]
III	15 [33.3]	13 [29.5]	0 [0.0]	29 [26.9]
IV	5 [11.1]	7 [15.9]	0 [0.0]	22 [20.4]
Multifocal neoplasia, n [%]	22 [28.9]	7 [13.5]	8 [21.1]	37 [19.6]
Prior dysplasia, n [%]	26 [32.9]	9 [16.4]	14 [36.8]	50 [26.5]
Indefinite for dysplasia	6 [7.6]	0 [0.0]	2 [5.3]	8 [4.2]
Low-grade dysplasia	24 [30.4]	8 [14.5]	14 [36.8]	47 [24.9]
Age at time of index AN in years, median [IQR]	48 [39.8-59.0]	62 [51.0-70.0]	58 [51.0-67.3]	55 [45.0-64.5]
IBD duration until index AN in years, median [IQR]	18.0 [11.0-24.0]	19.0 [13.0-31.0]	19.0 [13.0-30.0]	19.0 [12.0-26.0]
Endoscopic follow-up after index AN in months, median [IQR]	30.0 [0.0-61.0]	20.5 [1.0-40.5]	48.5 [13.0-104.5]	27.0 [7.0-69.0]
Endoscopies after index AN, median [IQR]	2 [0-4]	1.5 [0-3]	4 [2-6]	2 [1-4]

IBD: inflammatory bowel disease, IQR: interquartile range, PSC: primary sclerosing cholangitis, AN: advanced neoplasia.

[1] Including 17 patients without treatment of index AN.

[2] Risk classification prior to index AN, according to the BSG guidelines (20).

[3] For index CRC only, based on TNM classification (21).

Treatment of AN

Index advanced neoplasia was treated with (sub)total or proctocolectomy in 78 (41.3%; CD n=22, 33.8%; UC/IBD-U n=56, 45.2%) patients and with partial colectomy in 56 (29.6%; CD n=26, 40.0%; UC/IBD-U n=30, 24.2%) patients (table 2 and supplementary table 2). Endoscopic resection was performed in 38 (20.1%; CD n=12, 18.5%; UC/IBD-U n=26, 21.0%). There were no significant differences in patient characteristics between CD and UC/IBD-U, except for more frequent PSC in the (sub)total or proctocolectomy group and more extensive disease in the endoscopic resection group with UC (supplementary table 1). In 17 (9.0%; CD n=5, 7.7%; UC/IBD-U n=12, 9.7%) patients, the index advanced neoplasia was left untreated due to comorbidity or metastatic disease. Lesions were located in (previously) inflamed colonic mucosa in 76 (97.4%), 50 (89.3%) and 30 (78.9%) of patients who were treated with (sub)total or proctocolectomy, partial colectomy

or endoscopic resection, respectively. Indications for surgery are reported in supplementary table 3.

Table 2. Treatment of index advanced neoplasia

Treatment	HGD (n=81)	CRC (n=108)	Total sample (n=189)
(Sub)total or proctocolectomy, n [%]	**33 [40.7]**	**45 [41.7]**	**78 [41.3]**
Proctocolectomy	14 [17.3]	19 [17.6]	33 [17.5]
(Sub)total colectomy	19 [23.5]	26 [24.1]	45 [23.8]
Partial colectomy, n [%]	**12 [14.8]**	**44 [40.7]**	**56 [29.6]**
Left hemicolectomy	1 [1.2]	3 [2.8] 3	4 [2.1]
Right hemicolectomy	5 [6.2]	14 [13.0]	19 [10.1]
Segment resection	5 [6.2]	24 [22.2]	29 [15.3]
Ileocecal resection	1 [1.2]	3 [2.8]	4 [2.1]
Endoscopic resection, n [%]	**35 [43.2]**	**3 [2.8]**	**38 [20.1]**
Polypectomy	21 [25.9]	1 [0.9]	22 [11.6]
EMR	6 [7.4]	0 [0.0]	6 [3.2]
ESD	6 [7.4]	0 [0.0]	6 [3.2]
Unknown	2 [2.5]	2 [1.9]	4 [2.1]
No resection, n [%]	**1 [1.2]**	**16 [14.8]**	**17 [9.0]**

HGD: high-grade dysplasia, CRC: colorectal cancer, EMR: endoscopic mucosal resection, ESD: endoscopic submucosal dissection.

Synchronous CRC

Synchronous neoplasia (any grade) was found in 43 (22.8%, indefinite/low-grade dysplasia n=33, HGD n=9, CRC n=1), without a significant difference between CD (n=16, 13.9%) and UC/IBD-U (n=27, 29.4%, p=0.43). Synchronous neoplasia was observed in 22 (28.2%) patients who underwent (sub)total or proctocolectomy, 8 (14.3%) who underwent partial colectomy, and 13 (34.2%) who underwent endoscopic resection (p=0.06). Synchronous advanced neoplasia was found in 10 (5.3%) patients without a significant difference between CD (n=5, 3.4%) and UC/IBD-U (n=5, 6.6%, p=0.29). Synchronous advanced neoplasia was detected in 5 (6.4%) patients who underwent (sub)total or proctocolectomy, one (1.8%) who underwent partial colectomy and four (10.5%) who underwent endoscopic resection (figure 1).

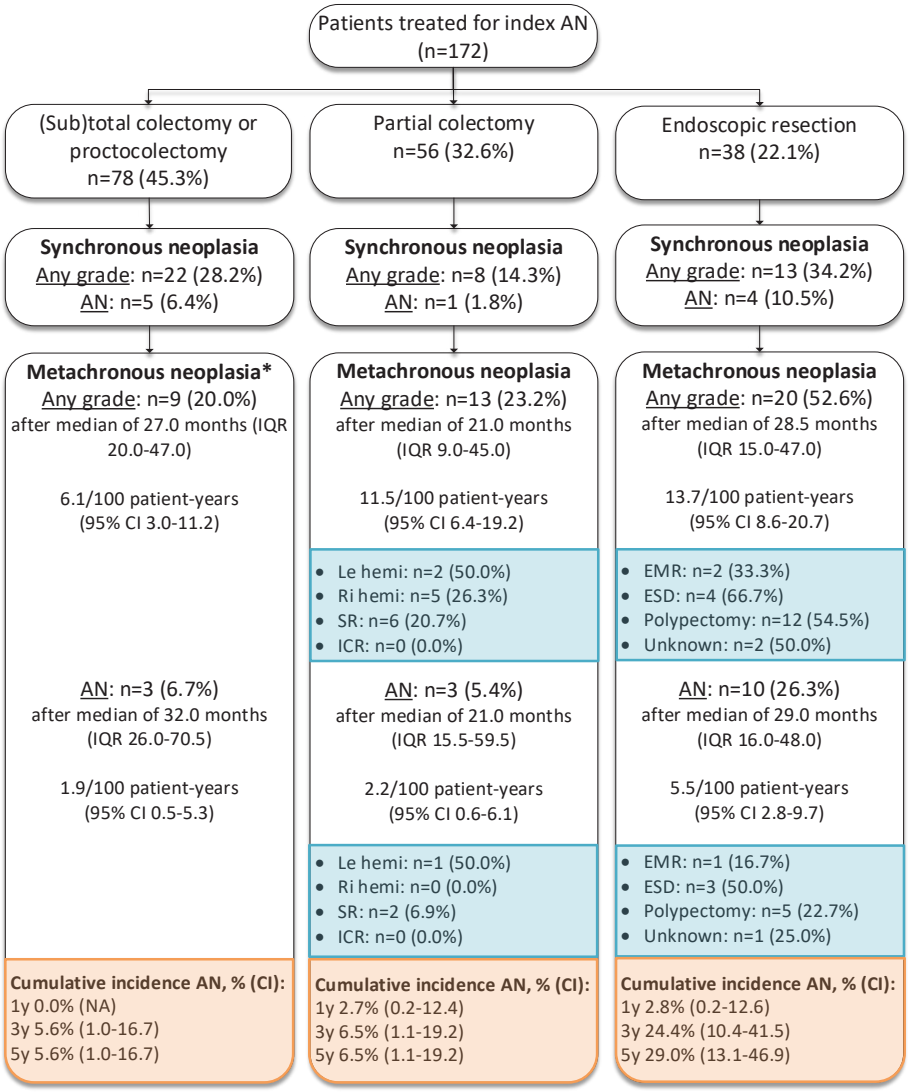


Figure 1. Synchronous and metachronous neoplasia per treatment modality

CRC: colorectal cancer, AN: advanced neoplasia, IQR: interquartile range, CI: confidence interval, NA: not applicable, Le hemi: left hemicolectomy, Ri hemi: right hemicolectomy, SR: segmental resection, ICR: ileocecal resection, EMR: endoscopic mucosal resection, ESD: endoscopic submucosal dissection.

[1] Seventeen patients who did not undergo treatment for index AN were excluded from analysis

[2] Patients who were treated with proctocolectomy were excluded from analysis of metachronous neoplasia.

Metachronous neoplasia

Median endoscopic follow-up after treatment of index advanced neoplasia was 27 months (IQR 7.0-69.0), with a median of two (IQR 1-4) endoscopies. Forty-two patients (30.2%, CD n=16, 24.6%; UC n=26, 21.0%) developed metachronous neoplasia (indefinite/low-grade dysplasia n=26, HGD n=9, CRC n=7) after median 27.5 months (IQR 14.0-46.0) (figure 2A). Overall metachronous (advanced) neoplasia rates and cumulative incidences for each treatment modality are displayed in figure 1. For CD, we found a metachronous neoplasia rate of 3.5, 9.2 and 16.9, and for UC/IBD-U of 7.8, 13.6 and 12.4 per 100 patient-years after (sub)total colectomy, partial colectomy and endoscopic resection, respectively (supplementary figure 2). Sixteen (11.5%, CD n=6, 9.2%; UC/IBD-U n=10, 8.1%) patients developed metachronous advanced neoplasia after median 28.0 months (IQR 17.5-55.0) (figure 2.b). We observed a metachronous advanced neoplasia rate of 3.2, 1.6 and 2.9 for CD and 1.1, 2.9 and 7.0 per 100 patient-years for UC/IBD-U after (sub)total colectomy, partial colectomy and endoscopic resection, respectively (supplementary figure 3).

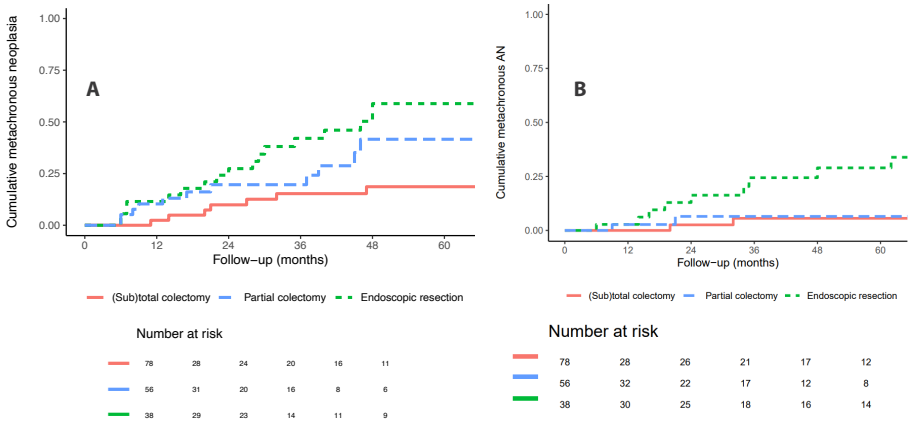


Figure 2. (A) Cumulative incidence of metachronous neoplasia by treatment modality. (B) Cumulative incidence of metachronous advanced neoplasia by treatment modality

Predictors of metachronous neoplasia

Our competing risk model showed that endoscopic resection was an independent predictor of metachronous neoplasia after adjustment for type of index advanced neoplasia, synchronous neoplasia and strictures or fistulas (asHR 3.56 (95% CI 1.50-8.43), p<0.01) in contrast to partial colectomy (asHR 2.00 (95% CI 0.82-4.89), p=0.13, table 3). Endoscopic resection was a predictor for metachronous advanced neoplasia (sHR 5.79 (95% CI 1.62-20.70), p<0.01, table 4). IBD type was not a significant effect modifier for the metachronous (advanced) neoplasia risk (data not

shown). A time-frame analysis, excluding patients with advanced neoplasia <2010, showed a statistically significant sHR in line with the main analysis (sHR 7.10, 95% CI 1.92-26.30, p<0.01). Of note, 12 (75.0%) metachronous lesions detected after endoscopic resection of index advanced neoplasia were located in the same colon segment where the index advanced neoplasia was found. Fifteen (35.7%) patients underwent additional surgical resection for metachronous neoplasia (supplementary figure 4).

Table 3. Univariable and multivariable hazard ratios for metachronous neoplasia (any grade)

Characteristics	Univariable sHR [95% CI]	P-value	Multivariable[1] asHR [95% CI]	P-value
Treatment				
Endoscopic	4.38 (2.01-9.56)	**<0.01**	3.56 (1.50-8.43)	**<0.01**
Partial colectomy (ref. (sub)total colectomy)	1.70 (0.74-3.93)	0.22	2.00 (0.82-4.89)	0.13
IBD type (ref: UC/IBD-U)	0.84 (0.44-1.58)	0.58		
Index AN (HGD)	2.29 (1.25-4.21)	**<0.01**		
Tumor stage[2] (ref: I)				
II	1.09 (0.33-3.59)	0.89		
III	0.50 (0.12-2.15)	0.35		
IV	0.19 (0.03-1.60)	**0.13**		
Synchronous neoplasia	2.29 (1.22-4.30)	**<0.01**		
Polypoid index AN[3] (ref non-polypoid or invisible)	0.80 (0.42-1.55)	0.52		
Prior dysplasia	1.00 (0.49-2.04)	0.99		
Extensive disease[4]	0.93 (0.48-1.77)	0.81		
Strictures or fistulas	0.57 (0.30-1.09)	0.09		
PSC	1.04 (0.41-2.66)	0.93		
Family history of CRC	1.64 (0.74-3.64)	0.23		
Age at time of index AN	1.00 (0.98-1.02)	0.97		
Disease duration at time of index AN	0.99 (0.97-1.02)	0.63		

sHR: subdistribution hazard ratio, CI: confidence interval, asHR: adjusted subdistribution hazard ratio, IBD: inflammatory bowel disease, UC: ulcerative colitis, IBD-U: IBD unclassified, HGD: high-grade dysplasia, PSC: primary sclerosing cholangitis, CRC: colorectal cancer.

[1] Multivariable model with adjustment for type of index AN, synchronous neoplasia and strictures or fistulas.

[2] For index CRC patients only.

[3] Thirty-four patients with missing values were not included in analysis.

[4] UC: E3 colitis (Montreal classification), CD: >50% inflamed colonic mucosa.

Mortality after CRC diagnosis

No significant difference in all-cause mortality between treatment modalities was observed after a median 70.0 months (IQR 32.8-98.5) follow-up (CRC: p=0.546, figure 3). All 17 patients who did not undergo treatment for index AN died within 3 years after index AN diagnosis.

Associations with treatment modalities

Compared to (sub)total or proctocolectomy, endoscopic resection and partial colectomy were more frequently performed in patients with limited disease extent (aOR 4.52, 95% CI 1.77-11.57, p=0.04 and aOR 3.49, 95% CI 1.09-11.24, p<0.01, respectively) and older age at time of index advanced neoplasia (annual aOR 1.06, 95% CI 1.02-1.09, p<0.01 and annual OR 1.08, 95% CI 1.03-1.13, p<0.01, respectively). Partial colectomy was associated with CD rather than UC/IBD-U (OR 2.21, 95% CI 1.07-4.53, p=0.03) and absence of PSC (aOR 8.94, 95% CI 1.09-73.5, p=0.04). Endoscopic resection was associated with HGD rather than CRC diagnosis (aOR 27.26, 95% CI 6.79-109.43, p<0.01, table 5).

Table 4. Univariable hazard ratios for metachronous advanced neoplasia.

Characteristics	Univariable sHR [95% CI]	P-value
Treatment		
Endoscopic	5.79 (1.62-20.70)	**<0.01**
Partial colectomy	1.11 (0.28-5.40)	0.90
(ref: (sub)total colectomy)		
IBD type	0.77 (0.27-2.20)	0.62
(ref: UC/IBD-U)		
Index AN (HGD)	4.34 (1.40-13.40)	**0.01**
Synchronous neoplasia	1.62 (0.57-4.58)	0.37
Polypoid index AN[1]	1.33 (0.47-3.80)	0.60
(ref non-polypoid or invisible)		
Prior dysplasia	1.50 (0.52-4.30)	0.45
Extensive disease[2]	6.66 (0.89-49.70)	0.06
Strictures or fistulas	0.30 (0.09-1.05)	0.06
PSC	1.10 (0.25-4.86)	0.90
Family history of CRC	2.74 (0.89-8.45)	0.08
Age at time of index AN	1.00 (0.96-1.03)	0.80
Disease duration at time of index AN	1.01 (0.98-1.05)	0.50

sHR: subdistribution hazard ratio, CI: confidence interval, IBD: inflammatory bowel disease, UC: ulcerative colitis, IBD-U: IBD unclassified, HGD: high-grade dysplasia, AN: advanced neoplasia, PSC: primary sclerosing cholangitis, CRC: colorectal cancer.

[1] Thirty-four missing values were not included in analysis.

[2] UC: E3 colitis (Montreal classification), CD: >50% inflamed colonic mucosa.

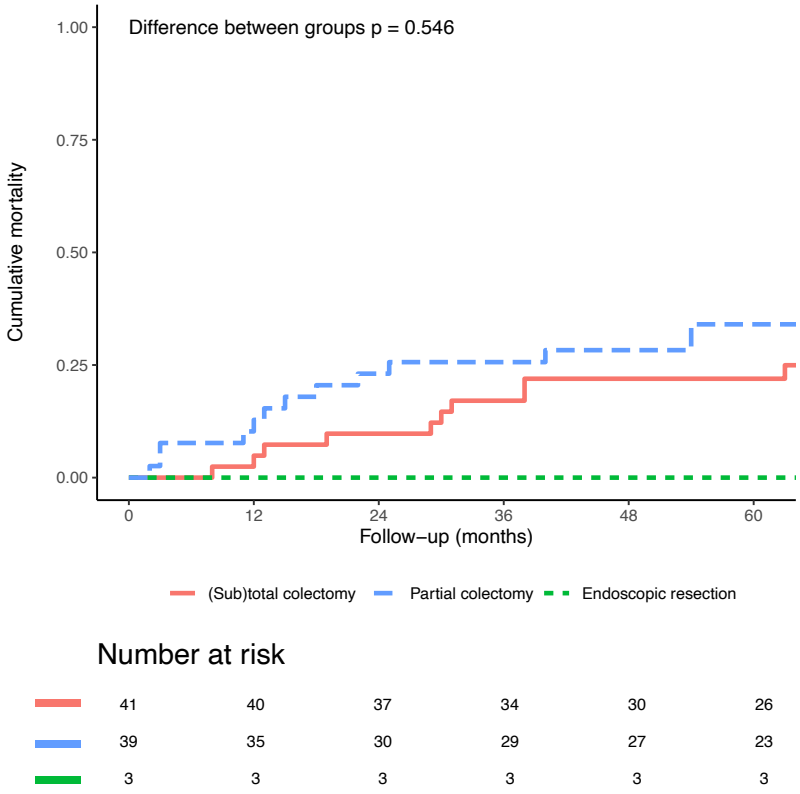


Figure 3. Cumulative all-cause mortality by treatment modality

Table 5. Multinomial regression results for characteristics associated with treatment modality of index advanced neoplasia (endoscopic vs. partial colectomy vs. (sub)total or proctocolectomy). (Sub)total or proctocolectomy was used as reference group.

Characteristics		Univariable OR [95% CI]	P-value	Multivariable OR [95% CI]	P-value
IBD type (Crohn's disease)	PC	2.21 [10.7-4.53]	0.03		
	ER	1.18 [0.51-2.73]	0.71		
Limited disease extent	PC	6.33 [2.72-14.75]	<0.01	4.52 [1.77-11.57]	0.04
	ER	3.54 [1.38-9.08]	<0.01	3.49 [1.09-11.24]	<0.01
Absence of pseudopolyps	PC	1.09 [0.54-2.17]	0.82		
	ER	1.12 [0.51-2.45]	0.78		
No family history of CRC	PC	0.72 [0.24-2.11]	0.55		
	ER	0.64 [0.20-2.06]	0.45		
No fistulas or stricture	PC	0.58 [0.29-1.17]	0.13		
	ER	1.23 [0.53-2.86]	0.64		
No perianal disease	PC	0.47 [0.18-1.25]	0.13		
	ER	0.13 [0.33-5.34]	0.68		
Absence of PSC	PC	15.33 [1.97-119.0]	<0.01	8.94 [1.09-73.5]	0.04
	ER	3.25 [0.89-11.88]	0.08	2.73 [0.63-11.87]	0.18
No prior dysplasia	PC	2.61 [1.11-6.14]	0.03		
	ER	0.86 [0.38-1.93]	0.71		
Index AN (HGD)	PC	0.37 [0.17-0.81]	0.01	0.62 [0.25-1.52]	0.30
	ER	15.91 [4.51-56.19]	<0.01	27.26 [6.79-109.43]	<0.01
Unifocal AN[1]	PC	2.62 [1.03-6.70]	0.04		
	ER	1.53 [0.61-3.85]	0.37		
Polypoid lesion[2]	PC	2.13 [0.93-4.87]	0.08		
	ER	7.98 [3.25-19.57]	<0.01		
Age at time of index AN, (per year increase)	PC	1.08 [1.05-1.12]	<0.01	1.06 [1.02-1.09]	<0.01
	ER	1.07 [1.03-1.11]	<0.01	1.08 [1.03-1.13]	<0.01
Academic centre	PC	0.22 [0.09-0.56]	<0.01		
	ER	0.51 [0.17-1.52]	0.23		

OR: odds ratio, CI: confidence interval, PC: partial colectomy, ER: endoscopic resection, CRC: colorectal cancer, PSC: primary sclerosing cholangitis, AN: advanced neoplasia.

[1] Six patients with missing values were not included in analysis

[2] Thirty-four missing values were not included in analysis

Discussion

In this multicenter study, including 189 IBD patients with advanced neoplasia, both partial colectomy and endoscopic resection were frequently performed in CD and UC/IBD-U. Synchronous neoplasia was detected in one-fourth of patients without significant differences between treatment modalities or IBD types. After confounder adjustment, partial colectomy did not result in an increased metachronous neoplasia risk compared to (sub)total colectomy. By contrast, endoscopic resection was associated with metachronous neoplasia and advanced neoplasia. IBD type did

not impact metachronous (advanced) neoplasia rates. All-cause mortality after CRC diagnosis did not differ between treatment modalities. Both endoscopic resection and partial colectomy were associated with limited disease extent and older age at time of index advanced neoplasia.

Current guidelines recommend (sub)total or proctocolectomy for advanced neoplasia in both CD and UC/IBD-U based on high synchronous and metachronous advanced neoplasia rates in previous studies [13,21,27]. We found synchronous advanced neoplasia in 3.4% of CD patients and 6.6% of UC patients treated with (sub)total or proctocolectomy. A recent Italian study in CD patients reported a higher advanced neoplasia rate of 9% after (sub)total or proctocolectomy [10]. Another observational UC study observed a higher synchronous advanced neoplasia rate of 14% [18]. Our study yielded a cumulative metachronous advanced neoplasia incidence of 6.7% after median 32.0 months following (sub)total colectomy and 5.4% after median 21.0 months following partial colectomy. Conflicting evidence regarding metachronous lesions after advanced neoplasia treatment in IBD is available. As such, one study in CD patients (n=64) reported a cumulative metachronous CRC incidence of 40% following partial colectomy and 35% after (sub)total colectomy after median seven years [19]. Another CD study (n=99) reported 1.3% and 0.0% CRC rates after median 3.5 years, respectively [10]. A UC study (n=59) did not detect any metachronous CRC after (sub)total or partial colectomy for CRC with a median follow-up of seven years [11]. These conflicting results might be explained by analysis without risk adjustment for proctocolectomy, differences in follow-up duration and CRC risk profiles of included patients.

One could hypothesize that the segmental inflammation of CD permits a more limited resection compared to the continuous inflammatory pattern of UC. Consequently, partial colectomy in UC might result in an increased metachronous neoplasia risk due to residual inflamed colonic mucosa compared to CD. Interestingly, we observed that partial colectomy was frequently performed in UC patients (24.2%) without an increased risk of metachronous neoplasia compared to CD. Moreover, CD and UC patients that underwent partial colectomy had similar disease characteristics, including a similar disease extent and age. It could be suggested that historically non- or mildly inflamed colonic segments do not harbor an increased metachronous neoplasia risk, which might explain the comparable metachronous neoplasia rates between patients with (sub)total colectomy and partial colectomy in both UC and CD. The comparable metachronous neoplasia and advanced neoplasia rates between partial colectomy and (sub)total colectomy suggest that treatment with partial colectomy seems safe. Importantly, patients

who received partial colectomy were older and had limited disease extent compared to those who underwent (sub)total colectomy, indicating that partial colectomy could be considered in case of a lower residual CRC risk after colectomy and in absence of other CRC risk factors. In addition, older patients may have more comorbidities or a limited life expectancy, justifying more restricted resection.

A significantly higher metachronous (advanced) neoplasia rate was found in patients who underwent endoscopic resection compared to those who underwent (sub)total colectomy. This might be explained by the risk of incomplete endoscopic resection of index advanced neoplasia and by more residual colon at risk for advanced neoplasia development. Indeed, 75.0% of metachronous neoplasia after endoscopic resection developed in the same colon segment as the index advanced neoplasia. Only one cohort study reported on endoscopic treatment of HGD with EMR and ESD, showing a metachronous neoplasia rate of 17% and a metachronous advanced neoplasia rate of 9-13% after a follow-up of 40-68 months [28]. The higher rate in our study (26.3% after median 29.0 months) could be explained by our high-risk population and less frequent use of EMR and ESD. The limited data on EMR and ESD in advanced neoplasia warrants further research on metachronous neoplasia rates. Our findings underline that endoscopic advanced neoplasia treatment should only be considered if the lesion is endoscopically resectable and close surveillance is feasible without impairment of mucosal visualization due to, for example, chronic disease activity or pseudopolyps. We recommend a multidisciplinary approach with gastroenterology and a gastro-intestinal surgeon with expertise in IBD to carefully select the treatment modality based on individual patient characteristics. In line with guidelines, we suggest performing strict endoscopic surveillance 3-6 months for the first year after endoscopic treatment [13,29]. Longer subsequent intervals could be considered in case of negative colonoscopies.

This study has several strengths. First, our PALGA search made it possible to construct a unique large cohort of patients with advanced neoplasia in IBD, including a large proportion of patients with HGD. Most previous studies focused on CRC, leaving HGD a fairly under-researched topic. Second, we employed competing risk analyses to prevent overestimation of metachronous advanced neoplasia rates due to proctocolectomy or death during follow-up. Third, we collected extensive information on disease course, including long-term follow-up and mortality data. There are also limitations, most notably the retrospective design. Despite the multicenter design this study has a relatively limited sample size compared to non-IBD studies due to the low incidence of advanced neoplasia in IBD. Treatment decisions in clinical practice are based on a variety of factors. Although we adjusted

for multiple confounders in our analyses, residual confounding due to patient- or physician preferences could impact our results. Due to the limited number of metachronous advanced neoplasia, we were not able to assess independent associations. Separate multivariable competing risk analyses for CD and UC/ IBD-U could not be performed due to the limited group size. Nevertheless, patient characteristics between IBD types were similar, and there was no significant effect modification of IBD type on the metachronous (advanced) neoplasia risk. Considering the long time period of our study, advances in surveillance techniques over the years could impact our results. In order to account for this, we performed a time-frame analysis, showing results in line with the main analysis.

To conclude, partial colectomy yielded a comparable metachronous (advanced) neoplasia risk compared to (sub)total colectomy in a selected cohort of CD and UC patients. This underlines the consideration of this treatment modality for patients with limited disease extent without other risk factors. Endoscopic resection of advanced neoplasia is associated with a high risk of metachronous neoplasia and advanced neoplasia, emphasizing the importance of stringent endoscopic surveillance after treatment.

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Supplementary Material

Supplementary table 1. Baseline characteristics by treatment modality and IBD type.

Characteristics	Treatment modality	CD(n=65)	UC/IBD-U(n=124)	p-value
Male sex, n [%]	P/(S)TC	12 [54.5]	35 [62.5]	0.610
	PC	11 [42.3]	21 [70.0]	0.058
	ER	6 [50.0]	15 [57.7]	0.734
Age at time of IBD diagnosis, median [IQR]	P/(S)TC	26 [20.5-40.0]	29 [19.0-41.0]	0.790
	PC	32 [23.8-44.3]	44 [23.5-57.3]	0.178
	ER	27 [18.3-43.3]	38 [26.8-51.0]	0.114
Family history of colorectal cancer, n [%]	P/(S)TC	3 [17.6]	5 [13.5]	0.696
	PC	3 [14.3]	5 [25.0]	0.454
	ER	1 [9.1]	5 [29.4]	0.355
Smoking, n [%]	P/(S)TC	1 [4.5]	1 [1.8]	0.558
Current		4 [18.2]	6 [10.7]	
Past		13 [59.1]	38 [67.9]	
None				
Current	PC	2 [7.7]	1 [3.3]	0.552
Past		10 [38.5]	7 [23.3]	
None		10 [38.5]	15 [50.0]	
Current	ER	2 [16.7]	2 [7.7]	0.727
Past		5 [41.7]	8 [30.8]	
None		4 [33.3]	13 [50.0]	
PSC, n [%]	P/(S)TC	1 [4.5]	16 [28.6]	**0.030**
	PC	1 [3.8]	0 [0.0]	0.464
	ER	1 [8.3]	2 [7.7]	1.000
Post inflammatory polyps, n [%]	P/(S)TC	8 [36.4]	27 [48.2]	0.450
	PC	12 [46.2]	12 [40.0]	0.788
	ER	5 [41.7]	11 [42.03]	1.000
Extensive disease[1], n [%]	P/(S)TC	19 [86.4]	49 [87.5]	1.000
	PC	14 [53.8]	15 [30.0]	0.795
	ER	4 [33.3]	21 [80.8]	**0.009**
CRC risk classification[2], n [%]	P/(S)TC	4 [18.2]	4 [7.1]	0.509
Low risk		8 [36.4]	23 [41.1]	
Intermediate risk		8 [36.4]	25 [44.6]	
High risk		2 [9.1]	4 [7.1]	
No surveillance indication				
Low risk	PC	7 [26.9]	7 [23.3]	0.280
Intermediate risk		13 [50.0]	10 [33.3]	
High risk		4 [15.4]	5 [16.7]	
No surveillance indication		2 [7.7]	8 [26.7]	
Low risk	ER	15 [25.0]	14 [12.5]	0.314
Intermediate risk		25 [41.7]	44 [39.3]	
High risk		13 [21.7]	37 [33.0]	
No surveillance indication		7 [11.7]	17 [15.2]	

Supplementary table 1. Continued

Characteristics	Treatment modality	CD(n=65)	UC/IBD-U(n=124)	p-value
Index AN, n [%]				
High-grade dysplasia	P/(S)TC	9 [40.9]	24 [42.9]	1.000
Colorectal cancer		13 [59.1]	32 [57.1]	
High-grade dysplasia	PC	6 [23.1]	6 [20.0]	1.000
Colorectal cancer		20 [76.9]	24 [80.0]	
High-grade dysplasia	ER	12 [100.0]	23 [88.5]	0.538
Colorectal cancer		0 [0.0]	3 [11.5]	
Lesion characteristics, n [%]				
Polypoid	P/(S)TC	6 [30.0]	10 [20.8]	0.179
Nonpolypoid		14 [70.0]	31 [64.6]	
Invisible		0 [0.0]	7 [14.6]	
Polypoid	PC	7 [35.0]	9 [40.9]	0.121
Nonpolypoid		11 [55.0]	11 [50.0]	
Invisible		2 [10.0]	2 [9.1]	
Polypoid	ER	11 [91.7]	16 [61.5]	0.355
Nonpolypoid		1 [8.3]	10 [38.5]	
Invisible		0 [0.0]	0 [0.0]	
Tumor stage[3], n [%]				
I	P/(S)TC	1 [7.7]	7 [21.9]	0.448
II		7 [53.8]	8 [25.0]	
III		4 [30.8]	11 [34.4]	
IV		1 [7.7]	4 [12.5]	
I	PC	4 [20.0]	2 [8.3]	0.545
II		9 [45.0]	8 [33.3]	
III		5 [25.0]	8 [33.3]	
IV		2 [10.0]	5 [20.8]	
I	ER	0 [0.0]	3 [100.0]	0.290
II		0 [0.0]	0 [0.0]	
III		0 [0.0]	0 [0.0]	
IV		0 [0.0]	0 [0.0]	
Multifocal neoplasia, n [%]	P/(S)TC	9 [40.9]	13 [24.1]	0.169
	PC	2 [8.0]	5 [18.5]	0.422
	ER	3 [25.0]	5 [19.2]	0.689
Prior dysplasia, n [%]	P/(S)TC	8 [36.4]	18 [32.1]	0.792
	PC	4 [15.4]	5 [16.7]	1.000
	ER	3 [25.0]	11 [42.3]	0.472
Age at index AN diagnosis, median [IQR)	P/(S)TC	53 [41.3-59.0]	46 [38.5-58.5]	0.505
	PC	58 [51.0-65.0]	65 [50.8-72.5]	0.068
	ER	55 [48.0-61.8]	62 [51.8-68.3]	0.155
IBD duration until index AN in years, median [IQR]	P/(S)TC	19 [11.8-26.8]	18 [11.0-24.0]	0.621
	PC	19 [16.0-31.0]	20 [9.3-31.3]	0.599
	ER	27 [11.5-34.5]	18 [12.3-27.8]	0.297

Supplementary table 1. Continued

Characteristics	Treatment modality	CD(n=65)	UC/IBD-U(n=124)	p-value
Follow-up after index AN in months, median [IQR]	P/(S)TC	36.5 [13.0-72.8]	29.0 [0.0-60.0]	0.360
	PC	20.5 [10.5-46.8]	18.5 [0.0-39.5]	0.667
	ER	84.5 [19.3-107.8]	40.5 [12.8-98.3]	0.376
Endoscopies after index AN, median [IQR]	P/(S)TC	3 [1.8-5.3]	2 [0.0-4.0]	0.132
	PC	2 [1.0-3.0]	1 [0.0-4.0]	0.694
	ER	5 [2.3-6.8]	4 [2.0-6.0]	0.466

CD: Crohn's disease, UC: ulcerative colitis, IBD-U: IBD unclassified, P/(S)TC: (sub)total colectomy or proctocolectomy, PC: partial colectomy, ER: endoscopic resection, IQR: interquartile range, PSC: primary sclerosing cholangitis, AN: advanced neoplasia.

[1] According to Montreal classification: For CD: >50% colon involvement. For UC: E3.

[2] Risk classification prior to index AN, according to the BSG guidelines (20).

[3] For index CRC only, based on TNM classification (21).

Supplementary table 2. Treatment of index advanced neoplasia by IBD type

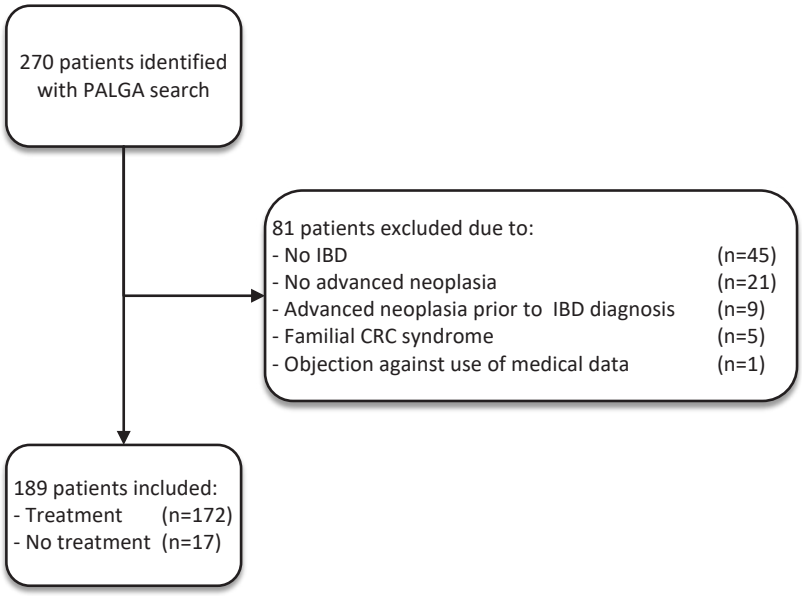
Treatment	CD (n=65)	UC/IBD-U (n=124)	Total sample (n=189)
(Sub)total or proctocolectomy, n [%]	22 [33.8]	56 [45.2]	78 [41.3]
Proctocolectomy	8 [12.3]	25 [20.2]	33 [17.5]
(Sub)total colectomy	14 [21.5]	31 [25.0]	45 [23.8]
Partial colectomy, n [%]	26 [40.0]	30 [24.2]	56 [29.6]
Left hemicolectomy	2 [3.1]	2 [1.6]	4 [2.1]
Right hemicolectomy	8 [12.3]	11 [8.9]	19 [10.1]
Segment resection	13 [20.0]	16 [12.9]	29 [15.3]
Ileocecal resection	3 [4.6]	1 [0.8]	4 [2.1]
Endoscopic resection, n [%]	12 [18.5]	26 [21.0]	38 [20.1]
Polypectomy	9 [13.8]	13 [10.5]	22 [11.6]
EMR	2 [3.1]	4 [3.2]	6 [3.2]
ESD	1 [1.5]	5 [4.0]	6 [3.2]
Unknown	0 [0.0]	4 [3.2]	4 [2.1]
No resection, n [%]	5 [7.7]	12 [9.7]	17 [9.0]

CD: Crohn's disease, UC: ulcerative colitis, IBD-U: IBD unclassified, EMR: endoscopic mucosal resection, ESD: endoscopic submucosal dissection.

Supplementary table 3. Indication per surgical treatment modality.

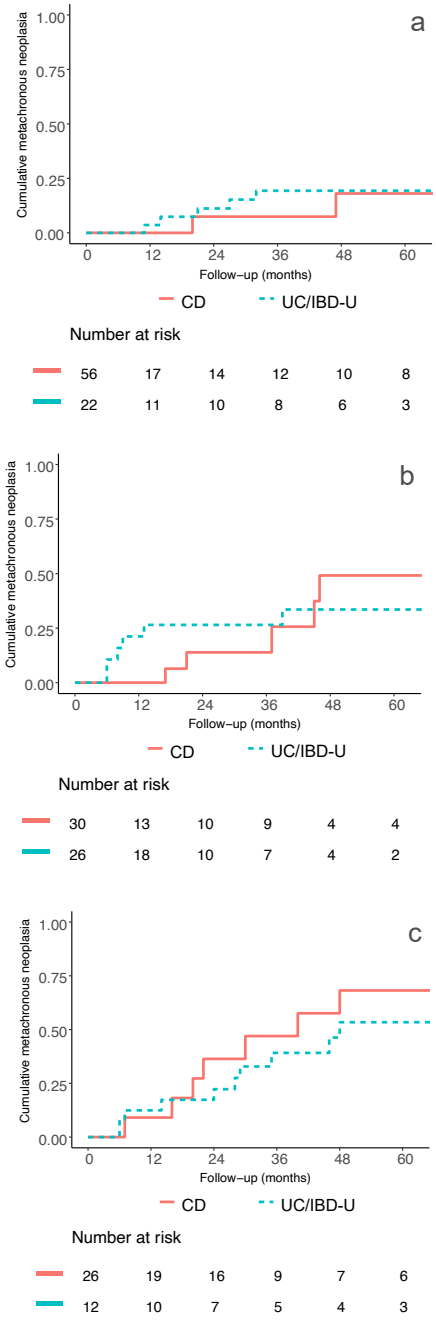
	Inflammation or stricture, n [%]	IND or LGD, n [%]	HGD, n [%]	CRC, n [%]
(Sub)total or proctocolectomy (n=78)	4 [5.1]	7 [9.0]	30 [38.5]	37 [47.4]
Proctocolectomy (n=33)	1 [3.0]	3 [9.1]	13 [39.4]	16 [48.5]
(Sub)total colectomy (n=45)	3 [6.7]	4 [8.9]	17 [37.8]	21 [46.7]
Partial colectomy (n=56)	6 [10.7]	2 [3.6]	9 [16.1]	39 [69.6]
Ileocecal resection (n=4)	1 [25.0]	1 [25.0]	0 [0.0]	2 [50.0]
Segmental resection (n=29)	2 [6.9]	1 [3.4]	4 [13.8]	22 [75.9]
Left hemicolectomy (n=4)	0 [0.0]	0 [0.0]	1 [25.0]	3 [75.0]
Right hemicolectomy (n=19)	3 [15.8]	0 [0.0]	4 [21.1]	12 [63.2]

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



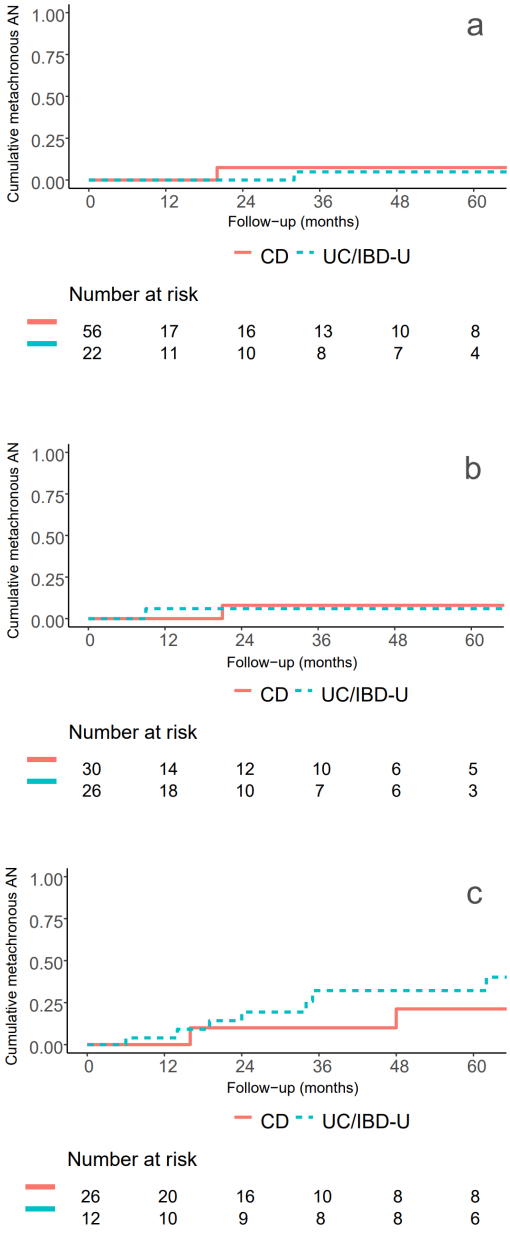
Supplementary figure 1. Flowchart patient selection

PALGA: The Dutch nationwide pathology databank, IBD: inflammatory bowel disease, CRC: colorectal cancer.



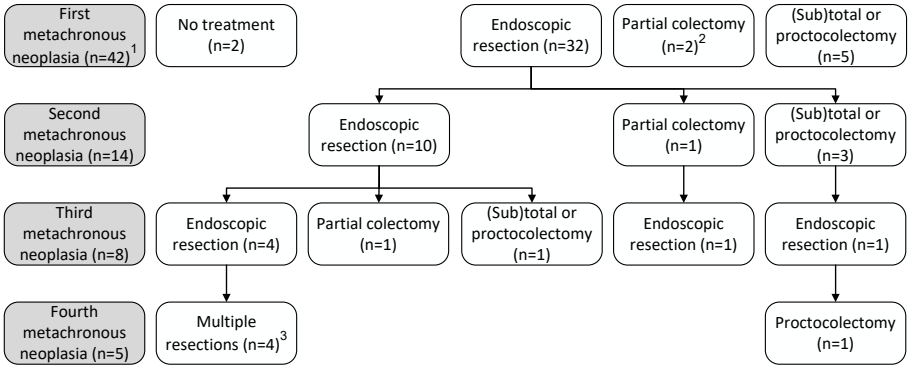
Supplementary figure 2. Cumulative incidence of metachronous neoplasia by IBD type for (a) (sub) total colectomy (b) partial colectomy and (c) endoscopic resection.

CD: Crohn's disease, UC: ulcerative colitis, IBD-U: IBD unclassified



Supplementary figure 3. Cumulative incidence of metachronous advanced neoplasia by IBD type for (a) (sub)total colectomy (b) partial colectomy and (c) endoscopic resection.

AN: advanced neoplasia, CD: Crohn's disease, UC: ulcerative colitis, IBD-U: IBD unclassified



Supplementary figure 4. Flowchart of treatment of metachronous neoplasia

[1] One case with missing data on treatment of metachronous neoplasia

[2] One patient with multiple subsequent metachronous lesions, treated with endoscopic resection and one more partial colectomy.

[3] Four patients with multiple subsequent metachronous lesions: Two eventually treated with endoscopic resection; one patient underwent two additional partial colectomies; and one patient had a partial colectomy and a (sub)total colectomy.

Chapter 5

High risk of colorectal cancer after high-grade dysplasia in inflammatory bowel disease patients

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Submitted

Abstract

Background and aims: There is limited data on colorectal cancer risk after high-grade dysplasia in inflammatory bowel disease. The aim of this study was to determine the long-term risk of colorectal cancer after a first diagnosis of high-grade dysplasia in inflammatory bowel disease, and to assess utilization of high-grade dysplasia treatment strategies over the past three decades.

Methods: In this nationwide retrospective cohort study, patients with colonic inflammatory bowel disease and high-grade dysplasia diagnosis between 1991 and 2021 were extracted from the Dutch nationwide pathology databank (PALGA). The primary outcome was the cumulative incidence of metachronous colorectal cancer. Kaplan Meier curves were used to show proctocolectomy free survival per decade.

Results: Colorectal cancer was diagnosed in 348 of 1,220 patients (28.5%). Of these, 204 patients (16.7%) were diagnosed with colorectal cancer within 6 months after the first high-grade dysplasia diagnosis and were considered synchronous colorectal cancer patients. Metachronous colorectal cancer was diagnosed in 144 of 1,016 patients (14.2%) after a median 3.6 years. The 1-, 5-, and 10-year cumulative incidences of metachronous colorectal cancer after high-grade dysplasia were 2.9%, 10.0%, and 15.9%, respectively. Proctocolectomy free survival did not differ between decades of high-grade dysplasia diagnosis.

Conclusion: The risk of synchronous and metachronous colorectal cancer after a diagnosis of high-grade dysplasia underlines the high-risk profile of this subgroup of inflammatory bowel disease patients. The possible advantages of colon sparing treatment should be balanced with the higher risk of metachronous colorectal cancer and the subsequent need for stringent endoscopic surveillance.

Keywords: inflammatory bowel disease; high-grade dysplasia; colorectal cancer

What you need to know

Background

Data on metachronous colorectal cancer risk and treatment modality after high-grade dysplasia in inflammatory bowel disease are limited.

Findings

The 1-, 5-, and 10-year cumulative incidences of metachronous colorectal cancer after high-grade dysplasia were 2.9%, 10.0%, and 15.9%, respectively. Endoscopic (vs surgical) treatment of high-grade dysplasia was associated with metachronous colorectal cancer.

Implications for patient care

The advantages of colon sparing treatment for high-grade dysplasia should be weighed against the higher risk of metachronous colorectal cancer and the subsequent need for stringent endoscopic surveillance.

Introduction

Patients with inflammatory bowel disease (IBD) are at increased risk of developing colorectal cancer (CRC) compared to the general population [1,2]. Chronic inflammation is considered the most important driver of carcinogenesis in IBD. Endoscopic surveillance is recommended to detect and remove colorectal neoplasia (CRN) and reduce CRC-related morbidity and mortality. Colonic high-grade dysplasia (HGD), with reported incidence rates of 1.0-3.5% in IBD, is the highest-risk precursor of CRC [3-6].

Although the risk of CRC after HGD is elevated in IBD patients, this observation is based on scarce and historical data, resulting in widely varying CRC rates (0.0-50.0%) [7-9]. Historically, colectomy was recommended for HGD given the high risk of invisible synchronous CRN. The implementation of advanced endoscopic imaging techniques have made previously invisible lesions detectable, possibly resulting in a lower advanced CRN risk [10-12]. This, together with advances in endoscopic resection techniques, facilitated a shift towards endoscopic treatment strategies to avoid colectomy [8,9,13,14]. In addition, there is limited information on CRC risk factors after developing HGD, hampering risk assessment in this specific high-risk group. Consequently, the optimal surveillance and treatment strategy for HGD in IBD remains uncertain.

In this nationwide study in IBD patients, we aimed to (1) determine the long-term risk of CRC and CRN after index HGD diagnosis, defined as the first diagnosis of colorectal HGD, (2) identify risk factors for metachronous CRC and CRN, and (3) research utilization of HGD treatment strategies over the past three decades.

Methods

Design and outcomes

We performed a nationwide retrospective cohort study to assess the following outcomes after index HGD diagnosis in IBD patients:

1) 1, 5 and 10 year cumulative incidences of metachronous CRC and CRN (including indefinite for dysplasia (IND), low-grade dysplasia (LGD), HGD and CRC)
2) Hazard ratios (HRs) of clinical and disease characteristics associated with metachronous CRC and CRN (any grade)
3) Applied HGD treatment strategies and proctocolectomy free survival per decade.

Study population

We used the Dutch nationwide pathology databank (PALGA) to identify IBD patients with a diagnosis of HGD between 1991 and 2021. PALGA has complete nationwide coverage since 1991. We included the following search terms for IBD: 'ulcerative colitis', 'Crohn's disease', 'indeterminate colitis', and 'chronic idiopathic inflammatory bowel disease', and for HGD: 'high-grade dysplasia', 'carcinoma in situ', and 'severe dysplasia' located in the colon or rectum. All patients with IBD and a histological diagnosis of HGD with available histological follow-up data were included. Patients with familial CRC syndromes or a diagnosis of CRC prior to index HGD diagnosis were excluded.

Data collection

Data extracted from PALGA included sex, age at index HGD diagnosis, IBD type, IBD duration at index HGD diagnosis, history of post-inflammatory polyps, strictures, primary sclerosing cholangitis, prior CRN, prior bowel surgery, and academic vs non-academic follow-up. In addition, we extracted data on index HGD, including location (ascending colon, transverse colon or descending colon), lesion shape (visible or invisible), multifocality and treatment strategy (type of endoscopic resection technique or surgical bowel resection). All endoscopic or surgical procedures within 6 months after index HGD diagnosis were considered treatment

of index HGD. Moreover, follow-up data on synchronous and metachronous CRN, including date, grade (IND, LGD, HGD or CRC), and treatment strategy were collected. Synchronous CRC was defined as a histological diagnosis of CRC within 6 months after index HGD diagnosis. All lesions diagnosed >6 months after index HGD were considered metachronous CRN. Patients with synchronous CRC were excluded from further analysis of metachronous CRC and CRN.

Statistical analysis

Categorical and continues variables were presented as proportions with percentages and medians with interquartile ranges (IQR), respectively. Differences between groups were assessed with the chi-square test, Student's t test, or nonparametric alternatives. A 2-tailed p-value of <0.05 was considered statistically significant. The Bonferroni method was applied to correct for multiple testing where appropriate. Cumulative incidences of overall development of CRC, and metachronous CRC and CRN after index HGD diagnosis were shown in 1 minus Kaplan-Meier curves. Patients were censored if no event occurred at the end of follow-up, defined as the date of proctocolectomy or the last pathology report. We performed a time-frame analysis comparing cumulative incidences of patients with index HGD diagnosis prior to 2010 to patients with index HGD diagnosis in 2010 or later, using the log rank test. The cut-off-point was set on 2010 because of the implementation of HD equipment and dye-based and virtual chromoendoscopy around this year, and the implementation of CRC surveillance in the Dutch IBD guideline in 2008 [15-18]. We performed a sensitivity analysis excluding metachronous IND, since IND could represent reactive changes instead of true neoplasia. Associations with metachronous CRC and CRN (any grade) were assessed using Cox proportional hazards model and were presented as (adjusted) HRs with 95% confidence intervals (CI). Potential associations and confounders were selected based on clinical relevance [19]. The proportional hazards assumption was tested for all variables by visual inspection of log-minus-log survival plots and adding time-dependent covariates to the model. A p-value of <0.05 was considered statistically significant. Missing data on IBD duration, lesion shape and location were imputed by performing multiple imputations by chained equations (MICE), using predictive mean matching. Missing data was assumed to be missing at random. Variables included in the imputation model were sex, age at index HGD, IBD type, strictures, post-inflammatory polyps, prior non-advanced CRN, prior bowel surgery, year of index HGD diagnosis, multifocal index HGD, academic vs non-academic follow-up, and treatment strategy of index HGD. Statistical analyses were performed with SPSS version 29. Incidence rates of CRC and CRN (any grade) with 95% CIs were determined using OpenEpi software [20].

Ethical considerations

This study was approved by the institutional review board of the Radboud University Medical Center (2024-17445) and the scientific committee of PALGA (LZV2022-80).

Results

Patients

Our PALGA search yielded 2,641 patients, of whom 1,220 were available for inclusion (figure 1). The majority of patients was male (66.3%) and had a ulcerative colitis diagnosis (62.8%) (table 1). The median age at index HGD diagnosis was 61 year. Index HGD was treated endoscopically in 890 (73.0%) patients and surgically in 329 (26.9%) patients, including 67 (5.5%) with proctocolectomy (table 2). Patients had a median 8 colorectal pathology reports available. The cumulative follow-up of the entire cohort from index HGD until the last available pathology report was 8,426 patient-years, with a median follow-up of 5.2 years (95% CI 1.9-10.2), including 1,034 with a follow-up of ≥ 1 years, 627 of ≥ 5 years, and 312 of ≥ 10 years.

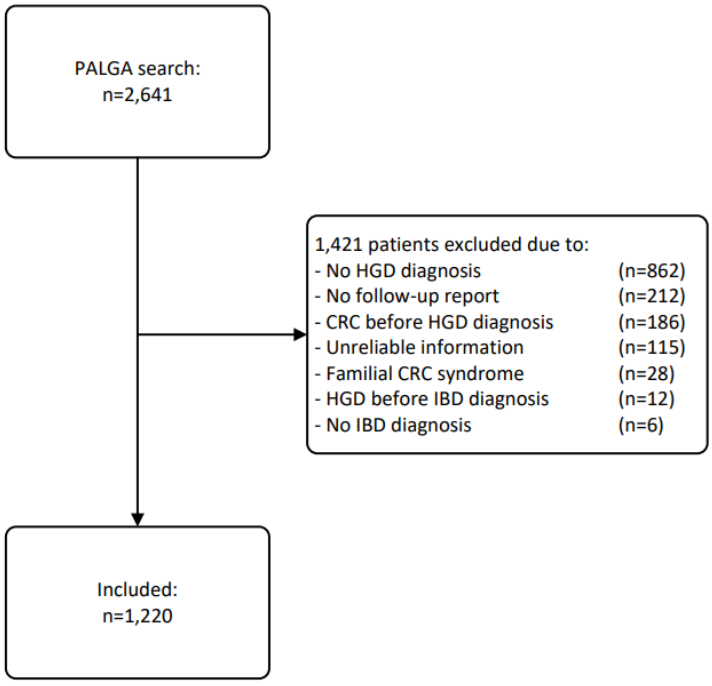


Figure 1. Flowchart patient selection

PALGA: Dutch Nationwide pathology databank, HGD: high-grade dysplasia, CRC: colorectal cancer, IBD: inflammatory bowel disease

Table 1. Baseline characteristics of n=1,220 HGD patients

Characteristics	No CRC (n=872)	Synchronous CRC (n=204)	Metachronous CRC (n=144)	Total (n=1,220)
Male sex, n [%]	580 [66.5]	131 [68.1]	131 [64.2]	809 [66.3]
Disease, n [%]				
Ulcerative colitis	548 [62.8]	113 [55.4]	105 [72.9]	766 [62.8]
Crohn's disease	222 [25.5]	64 [31.4]	30 [20.8]	316 [25.9]
IBD-unclassified	102 [11.7]	27 [13.2]	9 [6.3]	138 [11.3]
Post-inflammatory polyps, n [%]	191 [21.9]	49 [24.0]	46 [31.9]	286 [23.4]
Strictures, n [%]	79 [9.1]	47 [23.0]	23 [16.0]	149 [12.2]
Primary sclerosing cholangitis, n [%]	49 [5.6]	14 [6.9]	7 [4.9]	70 [5.7]
Prior neoplasia				
Indefinite for dysplasia	235 [26.9]	51 [25.0]	45 [31.3]	331 [27.1]
Low-grade dysplasia	11 [1.3]	4 [2.0]	2 [1.4]	17 [1.4]
Unknown non-advanced grade	203 [23.3] 21 [2.4]	43 [21.1] 4 [2.0]	35 [24.3] 8 [5.6]	281 [23.0] 33 [2.7]
Prior bowel surgery, n [%]				
Ileocecal resection	54 [6.3]	19 [9.3]	8 [4.9]	81 [6.6]
Segmental resection	15 [1.7]	3 [1.5]	2 [1.4]	20 [1.6]
Right hemicolectomy	15 [1.7]	3 [1.5]	1 [0.7]	19 [1.6]
Left hemicolectomy	7 [0.8]	1 [0.5]	0 [0.0]	8 [0.7]
Subtotal or total colectomy	1 [0.1] 16 [1.8]	0 [0.0] 12 [5.9]	0 [0.0] 5 [3.5]	1 [0.1] 33 [2.7]
Age at index HGD diagnosis, median [IQR]	62 [52-69]	61 [48-69]	58 [46-68]	61 [50-69]
IBD duration at index HGD diagnosis in years, median [IQR]*	16.8 [8.6-25.0]	20.2 [12.7-27.9]	17.1 [9.6-25.0]	17.5 [9.3-25.5]
Location index HGD, n [%]*	155.7 [17.9]	42.7 [20.9]	21.9 [15.2]	220.3 [18.1]
Ascending colon	85.5 [9.8]	26.7 [13.1]	14.8 [10.3]	127.0 [10.5]
Transverse colon	603.6 [69.2]	127.1 [62.3]	104.1 [72.3]	834.8 [68.4]
Descending colon	27.3 [3.1]	7.5 [3.7]	3.3 [2.3]	38.0 [3.1]
Multiple segments				
Visible index HGD, n [%]*	816.6 [93.6]	188.1 [92.2]	122.7 [85.2]	1127.4 [92.4]
Visible	55.4 [6.4]	15.9 [7.8]	21.3 [14.8]	92.6 [7.6]
Invisible				
Multifocal index HGD, n [%]	266 [30.5]	52 [25.5]	38 [26.4]	356 [29.2]
Indefinite for dysplasia	5 [0.6]	1 [0.5]	1 [0.6]	7 [0.6]
Low-grade dysplasia	174 [20.0]	31 [15.2]	21 [14.6]	226 [18.5]
High-grade dysplasia	87 [10.0]	20 [9.8]	16 [11.1]	123 [10.1]
Year of index HGD diagnosis, median [IQR]	2008 [2002-2012]	2010 [2004-2015]	2002 [1995-2009]	2007 [2001-2012]
Procedures with pathology report, median [IQR]	7 [5-11]	8 [6-12]	12 [8-16]	8 [5-12]

Table 1. Continued

Characteristics	No CRC (n=872)	Synchronous CRC (n=204)	Metachronous CRC (n=144)	Total (n=1,220)
Follow-up after index HGD in years, median [IQR]	5.5 [1.8-10.2]	3.3 [1.3-7.1]	7.1 [2.7-14.9]	5.2 [1.9-10.2]
Academic follow-up, n [%]	368 [42.2]	111 [54.4]	82 [56.9]	563 [46.0]

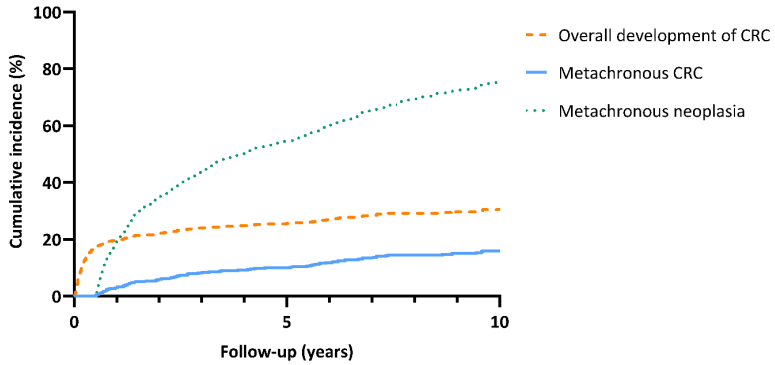
CRC: colorectal cancer, HGD: high-grade dysplasia, IBD: inflammatory bowel disease, IQR: interquartile range

* Pooled value of multiple imputation datasets. IBD duration at index HGD: 81.7% missing, location index HGD: 9.9% missing, Visible index HGD: 8.5% missing.

Table 2. Treatment index HGD within 6 months after index HGD diagnosis

Treatment index HGD	No CRC (n=872)	Synchronous CRC (n=204)	Metachronous CRC (n=144)	Total (n=1,220)
Endoscopic treatment	724 [83.0]	32 [15.7]	134 [93.1]	890 [73.0]
Surgery	148 [17.0]	172 [84.3]	10 [6.9]	329 [26.9]
Ileocecal resection	10 [1.1]	3 [1.5]	1 [0.7]	14 [1.1]
Segment resection	30 [3.4]	59 [28.9]	0 [0.0]	89 [7.3]
Right hemicolectomy	28 [3.2]	30 [14.7]	5 [3.5]	63 [5.2]
Left hemicolectomy	4 [0.5]	7 [3.4]	0 [0.0]	11 [0.9]
Subtotal or total colectomy	47 [4.7]	40 [19.6]	4 [2.8]	85 [7.0]
Proctocolectomy	35 [4.0]	33 [16.2]	0 [0.0]	67 [5.5]

HGD: high-grade dysplasia, CRC: colorectal cancer



Number at risk

- -	1220	509	247
—	1016	509	247
···	1016	311	103

Figure 2. Kaplan-Meier curves of the overall cumulative incidence of development of CRC after index HGD diagnosis (n=1,220, the orange striped line), the cumulative incidence of metachronous CRC (n=1,016, the blue line), and the cumulative incidence of metachronous CRN (n=1,016, the green dotted line).

CRC: colorectal cancer, HGD: high-grade dysplasia, CRN: colorectal neoplasia

Overall risk of developing CRC and synchronous CRC

CRC was diagnosed in 348 of 1,220 patients (28.5%) after a median 0.3 years, corresponding with an incidence rate of 5.2 (95% CI 4.7-5.8) per 100 patient-years. The 1-, 5- and 10-year cumulative incidences of CRC after HGD were 20.2%, 26.1% and 30.9%, respectively (figure 2). Of these, 204 patients (16.7%) were diagnosed with CRC within 6 months after index HGD diagnosis and were considered synchronous CRC patients. CRC was found in the same segment as index HGD in 257 patients (73.9%), including 190 synchronous CRC patients (93.1%).

Cumulative incidence of metachronous CRC

Metachronous CRC was diagnosed in 144 of 1,016 patients (14.2%) after a median 3.6 years, corresponding with an incidence rate of 2.2 (95% CI 1.8-2.5) per 100 patient-years. The 1-, 5- and 10-year cumulative incidences of metachronous CRC after HGD were 2.9%, 10.0% and 15.9%, respectively (figure 2).

Our timeframe analysis showed an incidence rate of 2.5 (95% CI 1.8-3.5) per 100 patient-years for patients with index HGD diagnosis in 2010 or later, which is similar to the incidence rate of patients with index HGD before 2010 (supplementary figure 1, $p = 0.34$).

Cumulative incidence of metachronous CRN (any grade)

Metachronous CRN developed in 638 patients (62.8%) after a median 2.2 years, corresponding with an incidence rate of 15.7 (95% CI 14.5-16.9) per 100 patient-years (figure 2). Of these, 12 patients developed IND as the highest grade of metachronous CRN, 243 LGD, 227 HGD and 144 CRC. The 1-, 5- and 10-year cumulative incidences of metachronous CRN were 18.3%, 54.0% and 75.2%, respectively. Twenty-five patients (41.7%) developed metachronous CRN in the residual rectum after subtotal colectomy, including 2 patients with IND as the maximum grade of CRN, 7 with LGD, 7 with HGD and 9 with CRC. Our sensitivity analysis excluding metachronous IND showed an incidence rate of 15.1 (95% CI 14.0-16.3) per 100 patient-years. The 1-, 5-, and 10-year cumulative incidences were 17.9%, 53.2%, and 74.7%.

Associations with metachronous CRC and CRN (any grade)

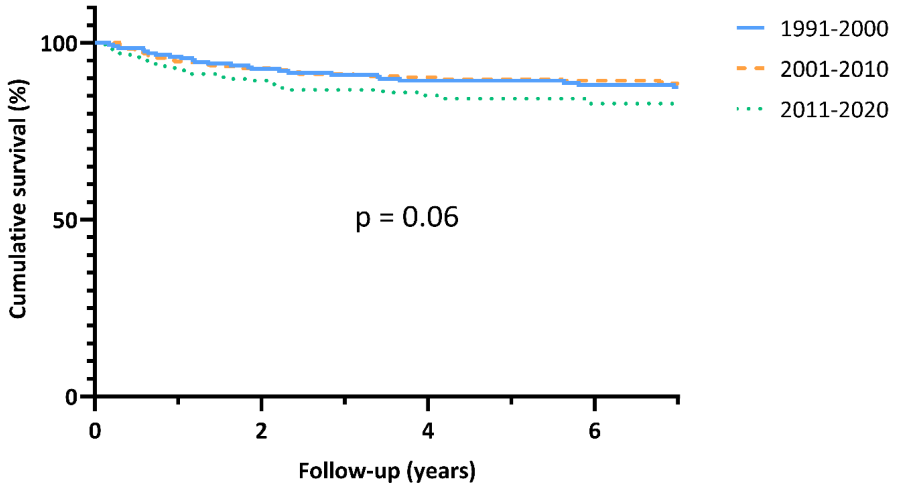
Post-inflammatory polyps (aHR 2.03, 95% CI 1.43-2.88, $p < 0.01$), prior IND or LGD (aHR 1.50, 95% CI 1.01-2.22, $p = 0.04$), invisible index HGD (aHR 2.25, 95% CI 1.34-3.78, $p < 0.01$), academic follow-up (aHR 1.49, 95% CI 1.05-2.12, $p = 0.03$), and endoscopic vs. surgical treatment (aHR 2.31, 95% CI 1.17-4.56, $p = 0.02$) were independent risk factors for metachronous CRC after index HGD diagnosis (table 3).

Table 3. Univariable and multivariable hazard ratios for metachronous CRC for n=1,016 patients

Characteristics	HR univariable [95% CI]	p-value	HR multivariable [95% CI]	p-value
Male sex	1.00 [0.71-1.42]	0.99	-	-
Disease[1]				
Ulcerative colitis	1.19 [0.79-1.79]	0.40	1.19 [0.79-1.79]	0.40
IBD-unclassified	0.66 [0.31-1.39]	0.27	0.66 [0.31-1.39]	0.27
(ref Crohn's disease)				
Post-inflammatory polyps[2]	2.03 [1.43-2.88]	<0.01	2.03 [1.43-2.88]	<0.01
Strictures[3]	1.68 [1.08-2.63]	0.02	1.54 [0.95-2.51]	0.08
Primary sclerosing cholangitis[4]	0.95 [0.44-2.03]	0.89	0.94 [0.44-2.01]	0.87
Prior neoplasia[5]	1.70 [1.19-2.43]	<0.01	1.50 [1.01-2.22]	0.04
Prior bowel surgery[6]	1.21 [0.59-2.47]	0.61	0.92 [0.41-2.05]	0.83
Age at index HGD diagnosis, per year increase[7]	1.00 [0.99-1.02]	0.86	1.00 [0.99-1.01]	0.95
Disease duration at index HGD diagnosis in years, per year increase[8]	1.02 [1.00-1.03]	0.10	1.02 [1.00-1.03]	0.10
Year index HGD diagnosis ≥2010	1.23 [0.81-1.86]	0.34	-	-
Right sided index HGD[9]	0.92 [0.56-1.50]	0.74	0.94 [0.57-1.54]	0.79
Invisible index HGD[10]	2.19 [1.34-3.60]	<0.01	2.25 [1.34-3.78]	<0.01
Multifocal index HGD[11]	0.98 [0.67-1.41]	0.89	0.91 [0.63-1.33]	0.64
Academic follow-up[12]	1.71 [1.23-2.38]	<0.01	1.49 [1.05-2.12]	0.03
Endoscopic treatment of index HGD[13] ***(vs surgical treatment)***	1.76 [0.92-3.35]	0.09	2.31 [1.17-4.56]	0.02

HR: hazard ratio, IBD: inflammatory bowel disease, HGD: high-grade dysplasia, PSC: primary sclerosing cholangitis, PIPs: post-inflammatory polyps.
Multivariable model with adjustment for:
[1] sex and PSC
[2] sex and age at index HGD diagnosis
[3] sex, IBD type, disease duration and invisible index HGD
[4] sex and IBD type
[5] sex, IBD type, PIPs, strictures, PSC, age at index HGD diagnosis and disease duration
[6] sex, IBD type, PIPs, strictures, PSC, age at index HGD diagnosis, disease duration, year of index HGD diagnosis
[7] sex, PSC, disease duration
[8] sex and PSC
[9] IBD type, PSC and prior bowel surgery
[10] PIPs, strictures, PSC, age at index HGD, disease duration, year of index HGD diagnosis
[11] sex, IBD type, PIPs, strictures, PSC, prior neoplasia, prior bowel surgery
[12] invisible index HGD, PSC, prior bowel surgery, treatment of index HGD, strictures, prior neoplasia, multifocal index HGD
[13] sex, IBD type, PIPs, strictures, PSC, prior neoplasia, prior bowel surgery, age at index HGD, disease duration, year of index HGD, location, invisible index HGD, multifocal index HGD, academic follow-up

In addition, post-inflammatory polyps (aHR 1.36, 95% CI 1.13-1.64, p < 0.01), primary sclerosing cholangitis (aHR 1.59, 95% CI 1.15-2.20, p < 0.01), prior IND or LGD (aHR 1.38, 95% CI 1.14-1.68, p < 0.01), age at index HGD diagnosis (aHR 1.01, 95% CI 1.01-1.02, p < 0.01), IBD duration at index HGD (aHR 1.01, 95% CI 1.00-1.01, p = 0.04), year of index HGD diagnosis in 2010 or later (HR 1.47, 95% CI 1.23-1.75, p < 0.01), multifocal index HGD (aHR 1.25, 95% CI 1.05-1.49, p = 0.01), academic follow-up (aHR 1.25, 95% CI 1.06-1.48, p < 0.01), and endoscopic treatment of index HGD (aHR 2.64, 95% CI 1.93-3.60, p < 0.01) were independent risk factors for metachronous CRN (supplementary table 1). Moreover, male sex (HR 0.78, 95% CI 0.66-0.93, p <0.01), was a protective factor for metachronous CRN.



Number at risk

1991-2000	217	179	157	143
2001-2010	447	353	291	243
2011-2020	313	175	97	58

HGD: high-grade dysplasia

Figure 3. Proctocolectomy free survival after index HGD diagnosis per decade

Treatment modalities per decade

Patients with index HGD diagnosis in 2011-2020 were older, with longer disease duration at index HGD diagnosis, and more often a diagnosis of Crohn's disease, prior neoplasia, post-inflammatory polyps, and multifocal index CRN, compared to previous decades (supplementary table 2). Endoscopic treatment was performed

in 185 (85.3%) patients with diagnosis of index HGD in 1991-2000, vs 378 (84.6%) in 2001-2010 and 258 (82.4%) in 2011-2020 (supplementary figure 2, p = 0.63). Proctocolectomy was performed in 162 (15.9%) patients after a median 5.3 (IQR 1.7-10.2) years after index HGD diagnosis. Proctocolectomy free survival did not differ between decades of index HGD diagnosis after 7 years of follow-up (figure 3, p = 0.06).

Discussion

In this nationwide cohort study, including 1,220 IBD patients with colorectal HGD, the 10-year cumulative incidences of metachronous CRC and CRN were 15.9% and 75.2%, respectively. Synchronous CRC was diagnosed in one out of six patients. Post-inflammatory polyps, prior IND or LGD, academic follow-up and endoscopic treatment of index HGD were associated with metachronous CRC and CRN.

Our study yielded an incidence rate of metachronous CRC of 14.2% after a median 3.6 years after HGD. In addition, we showed an incidence of overall development of CRC of 5.2 per 100 patient-years. A prior study from our group showed a combined HGD and CRC incidence rate of 11.5% after a median 2.3 years after index advanced neoplasia (n=81 HGD, n=108 CRC) depending on treatment strategy [8]. Other reported smaller cohorts (maximum n=48) included metachronous CRC rates after index HGD varying from 0.0 to 50.0% after a median 2.8 to 15.0 years, and an overall CRC rate of 23 per 100 patient-years [3,7,9]. These variations might be the result of differences in definition of metachronous CRC, study population (e.g. academic vs non-academic), and most importantly sample size. We found a high synchronous CRC rate of 16.7%, in line with previous studies that reported synchronous CRC rates of 11.4-33.3% [3,7]. This high risk of a CRC diagnosis within 6 months after HGD diagnosis indicates the need for clinical awareness and need for careful endoscopic assessment. Of note, we frequently found cases in which there was a high endoscopic suspicion for CRC, followed by a histopathological diagnosis of HGD. Moreover, 9 out of 10 synchronous CRCs were found in the same colonic segment as the index HGD lesion. This observation emphasizes the risk of sampling error and the challenging histopathological differentiation between HGD and CRC in IBD. Indeed, a previous study from our group showed an increased metachronous CRC risk after confirmation of histopathological HGD diagnosis by a second pathologist [21].

We found that post-inflammatory polyps, prior IND or LGD, academic follow-up and endoscopic vs surgical treatment of index HGD were associated with metachronous CRC and CRN, which is in line with previous studies on CRN risk in IBD [8,19,22]. Post-inflammatory polyps likely result from chronic active inflammation, and may therefore serve as a surrogate marker for disease severity, as was shown in two recent studies [23,24]. In contrast to previous reports, male sex was not identified as a risk factor in our cohort [19,22].

We did not find an increased proportion of endoscopic treatment of index HGD over time, nor did we find a higher proctocolectomy free survival. This could be explained by the longer disease duration, and the higher prior non-advanced neoplasia and multifocal index HGD rate in the last decade, making surgical treatment a more appropriate strategy. This in turn might be the result of expanding therapeutic options for IBD, delaying or even preventing colectomies performed for refractory disease. In line, a recent Dutch study showed an increased proportion of CRC in ulcerative colitis patients undergoing colectomy over time, although the absolute number of colonic resections did not change [25].

The findings of this study facilitate further CRC risk classification of this subgroup of IBD patients and may subsequently aid in selecting the appropriate treatment strategy for HGD.

Endoscopic techniques have become more refined over time, facilitating better lesion detection and resection, which may favor endoscopic resection as a treatment option for HGD. However, if high-quality endoscopic surveillance is not feasible or the patient is at high risk of metachronous CRC, colectomy should be considered.

Our study has several strengths. The nationwide design allowed us to build the largest HGD cohort in IBD to date in literature. We included over 1,200 patients, where the second largest cohort in literature comprised less than 100 HGD patients. We performed a time-frame analysis, to assess the possible change in metachronous CRC risk over time. There are also limitations. Data on IBD extent and severity were not available in the pathology database, limiting the ability to estimate the historic inflammatory burden per patient. Although numbers correspond with previous studies, there might be an underestimation of presence of post-inflammatory polyps, strictures and primary sclerosing cholangitis in our cohort, since these may not always be described in the clinical information of pathology reports [5,8,23,26]. Likewise, the endoscopic resection technique was frequently unspecified

in pathology reports. In addition, data on IBD duration was incomplete. In order to ensure adequate confounder correction, we performed data imputation in our multivariable analyses.

In conclusion, we found a high risk of synchronous and metachronous CRC after index HGD, underlining the high-risk profile of this subgroup of IBD patients. The advantage of endoscopic resection of HGD, including prevention of bowel surgery and preserving bowel function, should be carefully balanced with the higher risk of metachronous CRC and the subsequent need for stringent endoscopic surveillance.

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Supplementary tables and figures

Supplementary table 1. Univariable and multivariable hazard ratios for metachronous neoplasia (any grade) for n=1,016 patients

Characteristics	Univariable HRs [95% CI]	p-value	Multivariable HRs [95% CI]	p-value
Male sex	0.78 [0.66-0.93]	<0.01	-	-
Disease[1]	1.13 [0.94-1.37]	0.20	1.10 [0.91-1.33]	0.31
Ulcerative colitis	1.09 [0.81-1.45]	0.58	1.10 [0.82-1.47]	0.54
IBD-unclassified				
(ref Crohn's disease)				
Post-inflammatory polyps[2]	1.33 [1.10-1.60]	<0.01	1.36 [1.13-1.64]	<0.01
Strictures[3]	0.86 [0.66-1.12]	0.25	0.83 [0.62-1.10]	0.20
Primary sclerosing cholangitis[4]	1.65 [1.19-2.27]	<0.01	1.59 [1.15-2.20]	<0.01
Prior neoplasia[5]	1.53 [1.29-1.83]	<0.01	1.38 [1.14-1.68]	<0.01
Prior bowel surgery[6]	1.14 [0.82-1.60]	0.44	1.14 [0.78-1.67]	0.50
Age at index HGD diagnosis, per year increase[7]	1.01 [1.00-1.02]	<0.01	1.01 [1.01-1.02]	<0.01
Disease duration at index HGD diagnosis in years, per year increase[8]	1.01 [1.00-1.02]	0.06	1.01 [1.00-1.01]	0.04
Year index HGD diagnosis ≥2010	1.47 [1.23-1.75]	<0.01	-	-
Right sided index HGD[9]	0.97 [0.78-1.21]	0.81	0.93 [0.75-1.17]	0.54
Invisible index HGD[10]	0.96 [0.70-1.32]	0.79	1.05 [0.76-1.46]	0.77
Multifocal index HGD[11]	1.34 [1.13-1.60]	<0.01	1.25 [1.05-1.49]	0.01
Academic follow-up[12]	1.26 [1.08-1.48]	<0.01	1.25 [1.06-1.48]	<0.01
Endoscopic treatment of index HGD[13] ***(vs surgical treatment)***	1.97 [1.48-2.63]	<0.01	2.64 [1.93-3.60]	<0.01

HR: hazard ratio, IBD: inflammatory bowel disease, HGD: high-grade dysplasia, PSC: primary sclerosing cholangitis, PIPs: post-inflammatory polyps.
Multivariable model with adjustment for:
[1] sex and PSC
[2] sex and age at index HGD diagnosis
[3] sex, IBD type, disease duration and invisible index HGD
[4] sex and IBD type
[5] sex, IBD type, PIPs, strictures, PSC, age at index HGD diagnosis and disease duration
[6] sex, IBD type, PIPs, strictures, PSC, age at index HGD, disease duration, year of index HGD diagnosis
[7] sex, PSC, disease duration
[8] sex and PSC
[9] IBD type, PSC and prior bowel surgery
[10] PIPs, strictures, PSC, age at index HGD, disease duration, year of index HGD diagnosis
[11] sex, IBD type, PIPs, strictures, PSC, prior neoplasia, prior bowel surgery
[12] invisible index HGD, PSC, prior bowel surgery, treatment of index HGD, strictures, prior neoplasia, multifocal index HGD
[13] sex, IBD type, PIPs, strictures, PSC, prior neoplasia, prior bowel surgery, age at index HGD, disease duration, year of index HGD, location, invisible index HGD, multifocal index HGD, academic follow-up

Supplementary table 2. Baseline characteristics of n=977 patients per decade of index HGD

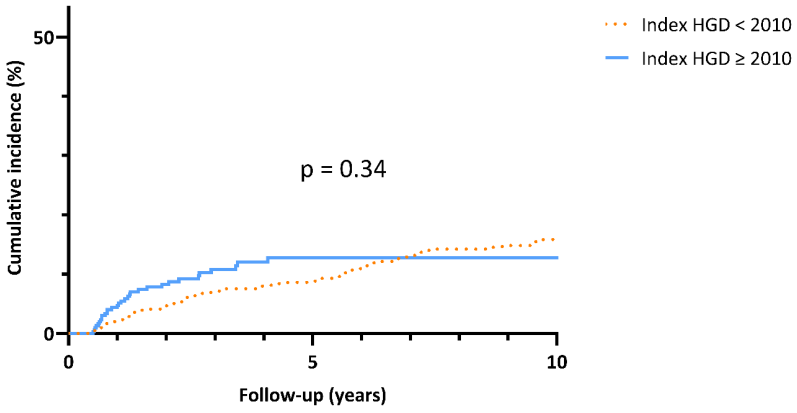
Characteristics	Total (n=977)	1991-2000 (n=217)	2001-2010 (n=447)	2011-2020 (n=313)	P-value[1]
Male sex, n [%]	650 [66.5]	145 [66.8]	306 [68.5]	199 [63.6]	0.37
Disease, n [%]	624 [63.9]	165 [76.0]	289 [64.7]	170 [54.3]	<0.01[2]
Ulcerative colitis	248 [25.4]	41 [18.9]	118 [26.4]	89 [28.4]	
Crohn's disease	105 [10.7]	11 [5.1]	40 [8.9]	54 [17.3]	
IBD-unclassified					
Post-inflammatory polyps, n [%]	231 [23.6]	47 [21.7]	94 [21.0]	90 [28.8]	0.04
Strictures, n [%]	97 [9.9]	19 [8.8]	43 [9.6]	35 [11.2]	0.63
Primary sclerosing cholangitis, n [%]	53 [5.4]	8 [3.7]	25 [5.6]	20 [6.4]	0.39
Prior neoplasia	13 [1.3]	2 [0.9]	5 [1.1]	6 [1.9]	<0.01[2]
Indefinite for dysplasia	230 [23.5]	23 [10.6]	95 [21.3]	112 [35.8]	
Low-grade dysplasia	28 [2.9]	14 [6.5]	14 [3.1]	0 [0.0]	
Unknown non-advanced grade					
Prior bowel surgery, n [%]	17 [1.7]	3 [1.4]	10 [2.2]	4 [1.3]	0.49
Ileocecal resection	16 [1.6]	4 [1.9]	8 [1.8]	4 [1.3]	
Segmental resection	7 [0.7]	1 [0.5]	2 [0.4]	4 [1.3]	
Right hemicolectomy	1 [0.1]	0 [0.0]	0 [0.0]	1 [0.3]	
Left hemicolectomy	19 [1.9]	3 [1.4]	6 [1.3]	10 [3.2]	
(Sub)total colectomy					
Age at index HGD diagnosis, median [IQR]	61 [51-69]	57 [47-67]	61 [51-69]	64 [56-71]	<0.01
IBD duration at index HGD diagnosis in years, median [IQR]*	17.0 [8.8-25.1]	14.5 [6.3-22.0]	16.6 [8.9-24.6]	19.2 [10.9-27.9]	0.02
Location index HGD, n [%]	173.5 [17.8]	26.8 [12.4]	80.6 [18.0]	66.2 [21.2]	0.07[2]
Ascending colon	96.0 [9.8]	19.7 [9.1]	45.7 [10.2]	30.6 [9.8]	
Transverse colon	677.7 [69.4]	155.7 [71.8]	312.3 [69.9]	209.6 [70.0]	
Descending colon	29.9 [3.1]	14.9 [6.9]	8.4 [1.9]	6.6 [2.1]	
Multiple segments					
Visible index HGD, n [%]*	906.7 [92.8]	195.7 [90.2]	412 [92.2]	299.0 [95.5]	0.06
Visible	70.3 [7.2]	21.3 [9.8]	35 [7.8]	14.0 [4.5]	
Invisible					
Multifocal index CRN, n [%]	6 [0.6]	0 [0.0]	2 [0.4]	4 [1.3]	<0.01[2]
Indefinite for dysplasia	184 [18.8]	24 [11.1]	71 [15.9]	89 [28.4]	
Low-grade dysplasia	102 [10.4]	31 [14.3]	48 [10.7]	23 [7.3]	
High-grade dysplasia					
Procedures with pathology report, median [IQR]	8 [5-12]	9 [6-14]	8 [5-12]	7 [4-10]	<0.01
Follow-up after index HGD in years, median [IQR]	5.7 [2.0-10.5]	11.5 [4.8-18.4]	7.0 [2.7-11.2]	2.6 [1.0-5.2]	<0.01
Academic, n [%]	427 [43.7]	106 [48.8]	196 [43.8]	125 [39.9]	0.13
Development of CRC	848 [86.8]	167 [77.0]	400 [89.5]	281 [89.8]	<0.01
No CRC	129 [13.2]	50 [23.0]	47 [10.5]	32 [10.2]	
Metachronous CRC					

CRC: colorectal cancer, HGD: high-grade dysplasia, IBD: inflammatory bowel disease, IQR: interquartile range.

[1] Chi-square for categorial variables and Kruskal Wallis for continues variables.

[2] Adjusted P-value after Bonferroni correction.

* Pooled value of multiple imputation datasets. IBD duration at index HGD: 78.4% missing, location index HGD: 10.7% missing, Visible index HGD: 7.6% missing.

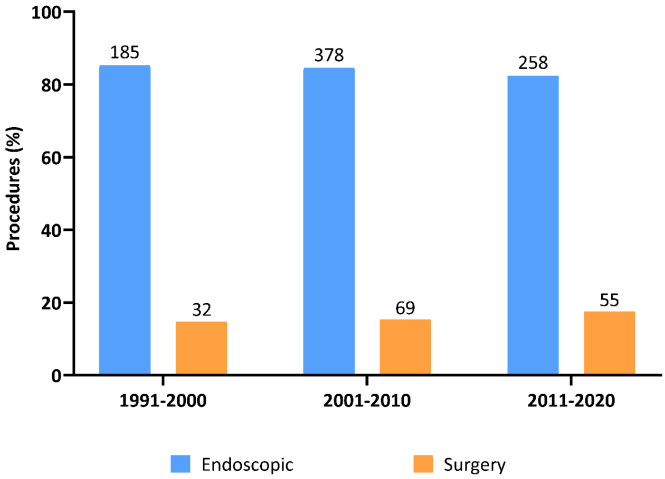


Number at risk

—	649	408	232
- -	367	101	15

CRC: colorectal cancer, HGD: high-grade dysplasia

Supplementary figure 1. Kaplan-Meier curves of the cumulative incidence of metachronous CRC after index HGD diagnosis for patients with index HGD diagnosis before 2010 vs in 2010 or later (n=1,016).



Supplementary figure 2. Endoscopic vs surgical treatment of index HGD per decade.
HGD: high-grade dysplasia

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Part III

Healthcare utilization

Chapter 6

Reduction in inflammatory bowel disease healthcare during the coronavirus disease 2019 pandemic: a nationwide retrospective cohort study

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Gastroenterology. 2021 Feb;160(3):935-937.e1

Introduction

Coronavirus disease 2019 (COVID-19) caused a worldwide disruption of regular health care, with more than 37 million cases and over 1,000,000 deaths [1]. After confirmation of the first COVID-19 patient in The Netherlands, a country with 17.4 million inhabitants and universal health care, on February 27, 2020, the pandemic rapidly spread across the country, reaching its first peak in April 2020 [2]. Regular health care, including inflammatory bowel disease (IBD) care, was strongly reduced to establish sufficient capacity for COVID-19 care and to prevent COVID19 spread by patients and healthcare workers.

IBD health care includes scheduled outpatient monitoring and endoscopic or surgical procedures. Because of decreased hospital capacity for non–COVID-19 care, many IBD-related appointments and procedures were canceled or postponed. In addition, initial confinement measures to prevent the spread of COVID-19 had an emphasis on safeguarding vulnerable populations, including IBD patients [3]. Most consultations for general practitioners transitioned to tele-health or did not take place at all because of flooding of practices by COVID-19 care. Finally, fear of COVID-19 increased the risk of delayed care-seeking behavior by patients, leading to less hospital visits [4].

The exact consequences of these factors on regular IBD health care are unknown. This information may provide guidance for patients and healthcare workers to prevent mortality and morbidity in the IBD population and could aid in improved healthcare management and prioritization during a new outbreak. Therefore, we aimed to determine the decrease in delivered IBD health care during the COVID19 pandemic of 2020 in comparison with national data from 2018 to 2019 by using a pathology database with full nationwide coverage.

Methods

We conducted a search (starting August 28, 2020) in PALGA (the nationwide network and registry of histo- and cytopathology in the Netherlands) to identify IBD-related endoscopies or surgery, new diagnoses of IBD, or IBD-related dysplasia and colorectal cancer (CRC) in a nationwide retrospective cohort study [5]. Incidences of these procedures and diagnoses were determined and displayed using graphs up to week 32 and compared with mean incidence data from 2018 to 2019. The COVID-19 pandemic in the Netherlands was defined as the period from

February 27, 2020 to August 9, 2020 (week 32) [2]. More details are provided in the Supplementary Methods.

Results

The PALGA search resulted in 66,684 IBD-related procedures, of which 61,097 procedures were eligible after exclusion of non-IBD diagnoses.

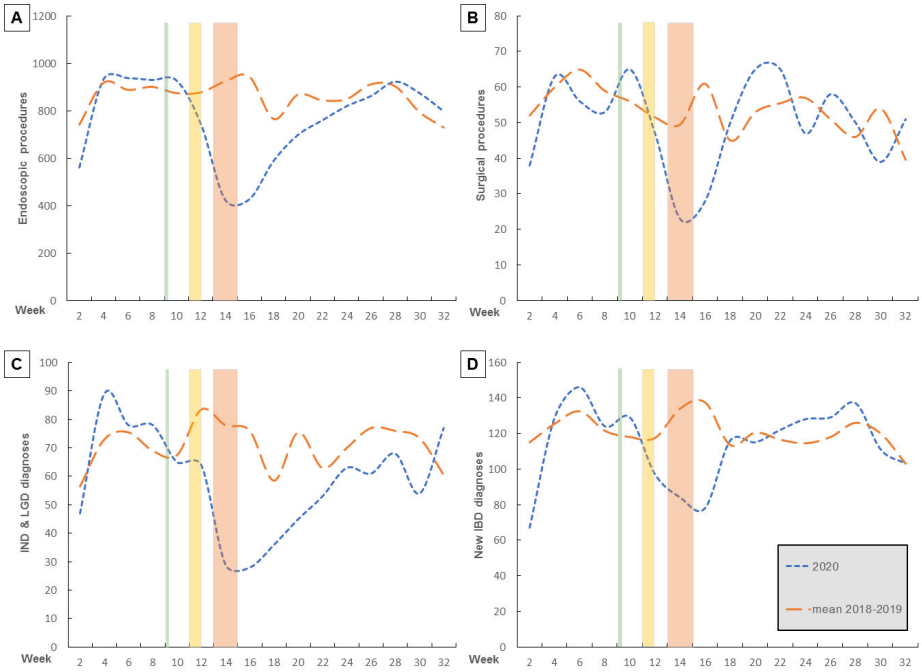

Figure 1. (A) Total IBD-related endoscopic procedures, (B) surgical procedures, (C) indefinite dysplasia and low-grade dysplasia (IND and LGD) diagnoses, and (D) new IBD diagnoses. Green bar, February 27, 2020, first case of COVID-19 in The Netherlands; yellow bar, nationwide confinement measures implementation; orange bar, peak of COVID-19–related hospitalizations in The Netherlands

IBD-related Procedures

A decline in total incidence of IBD-related procedures (endoscopy and surgery) was seen during the COVID-19 pandemic. At the national peak of the pandemic in April 2020, a maximum decrease of 59.7% (310 procedures) was observed compared with the mean incidence in April 2018 to 2019. Although a relative increase of IBD procedures was seen in the subsequent weeks, an overall decrease of 14.2% (1,476 procedures) was present for the total COVID-19 pandemic period compared with

the same period in 2018 to 2019. Endoscopic and surgical procedures showed a net decrease of 14.7% (1,443 procedures) and 5.5% (33 procedures), respectively (Figure 1).

New IBD Diagnoses and IBD-related Dysplasia or CRC

New IBD diagnoses during the COVID-19 pandemic decreased by 6.5% (125 diagnoses) compared with 2018 to 2019, with a maximum decrease of 46.3% (30 diagnoses). Indefinite and low-grade dysplasia diagnoses decreased by 25.5% (214 diagnoses). No decrease was seen for high-grade dysplasia or CRC diagnoses.

Discussion

In this nationwide retrospective cohort study we found a large reduction in IBD health care during the COVID-19 pandemic. At the height of the pandemic, almost 6 of 10 IBD-related procedures were canceled or postponed. Importantly, in the months of recovery after the peak of the pandemic this deficit was not fully compensated, leading to a net decrease in IBD-related procedures of approximately 14% compared with 2018 to 2019.

The decrease in IBD-related procedures was smaller for surgical procedures compared with endoscopic procedures (5.5% vs 14.7%). In addition, no decrease in high-grade dysplasia and CRC diagnoses was seen. Both can be explained by higher prioritization, because the indication for surgery is often based on high-grade dysplasia, CRC, or severe disease. Furthermore, these patients are more likely to present themselves with symptoms resulting from the underlying malignancy (anemia, rectal bleeding) than those with indefinite dysplasia or low-grade dysplasia, leading to timely referral.

Several clinical implications can be drawn from this study. First, the incomplete recovery of missed procedures and diagnoses implicates there are still patients with undiagnosed dysplasia at risk of progression to CRC. A recent study estimated that a 3-month delay in cancer surgery because of worldwide COVID-19 care reduces the benefit in life-years gained of all COVID-19 care by 19% [6]. This implies that optimization of healthcare management is needed to prevent negative outcomes for patients because of insufficient regular health care, including IBD health care. Second, the decrease in IBD-related procedures during the COVID-19 pandemic will allow evaluation of the current CRC surveillance practice. Further research into mortality and morbidity after the COVID-19 pandemic will open opportunities for appraisal and possible improvement of stratification and surveillance strategies.

This study has multiple strengths, including the use of the nationwide PALGA database with excellent national coverage, with confirmed accuracy for IBD and IBD-related diagnoses [7,8]. There are also limitations. First, our results represent the procedures where histology was acquired, excluding endoscopic procedures without tissue sent for histologic evaluation. However, this might correlate with an absence of need to obtain a biopsy specimen (no suspicion of dysplasia/CRC or inflammation), likely limiting the consequences of postponement for these patients. Second, because of the nature of PALGA, no data on type of endoscopy (surveillance or not), therapy, or mortality were available. Nevertheless, the true consequences of the COVID-19 pandemic on effective surveillance, therapy, and mortality are likely not measurable yet, opening possibilities for future research in the upcoming years.

In conclusion, in this nationwide study we observed a decrease in IBD endoscopy and surgery during the COVID-19 pandemic. Although the use of procedures has returned to comparable levels with preceding years, a deficit remains while the strong decrease in dysplasia diagnoses is concerning. These data may help healthcare providers and hospitals in planning health care during a second peak of COVID-19 in the near future.

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Supplementary Methods

Data Source

This study was approved by the nationwide network and registry of histopathology and cytopathology in The Netherlands' (PALGA) privacy commission and scientific council (lzv-2020-123). All data in this registry are pseudonymized with unique identifiers linked to individual patients. This registry has had complete national coverage since 1991. A search of the PALGA database is able to correctly identify 92% to 95% of all IBD patients, which was previously validated with individual patient records. The PALGA search was performed with the terms "ulcerative colitis," "Crohn's disease," "indeterminate colitis," and "chronic inflammatory bowel disease" for IBD, combined with a search of pathologists' report conclusions using similar terms.

Definitions

IBD diagnosis was based on histology results from biopsies or resection specimens. New IBD diagnoses were defined as absence of an historical PALGA report confirming IBD in combination with a present report with a PALGA diagnosis of IBD. IBD-related surgery and endoscopic procedures were defined by the type of PALGA report (e.g. a resection specimen or intestinal biopsy). Reports of individual patients from a single date were considered to be from the same procedure.

Inclusion and Exclusion Criteria

All IBD patients (with an established diagnosis of ulcerative colitis, Crohn's disease, or IBD unclassified) were eligible for inclusion. Exclusion criteria were a missing PALGA diagnosis of IBD in combination with absence of an IBD diagnosis in the pathologists' conclusion of the reports.

Data Collection

Extracted variables from the PALGA database were date of biopsy or resection, type of dysplasia (indefinite, low-grade, or high-grade dysplasia) or presence of CRC and new IBD diagnosis. A screening of all individual histology records was performed to exclude any false-positive IBD-related diagnoses.

Statistical Analysis

Incidence rates were assessed with SPSS version 25 (IBM, Armonk, NY). Because we used complete nationwide data, sampling error is not an issue for interpretation of results for The Netherlands. In relation to other countries struck by COVID-19, sampling error is likely to be small in comparison with major incidence influencing

factors like differences in confinement measures and healthcare policies. Therefore, we did not present confidence intervals or P values in this article because these only represent sampling error and could be misleading in this context.

Chapter 7

Long-term impact of the COVID-19 pandemic on inflammatory bowel disease healthcare utilization: a 2-year nationwide update

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Introduction

The coronavirus disease-19 (COVID-19) pandemic has profoundly impacted gastroenterology healthcare, with a considerable reduction in scheduled healthcare in the early phase of the pandemic [1-3]. Inflammatory bowel disease (IBD) healthcare depends on frequent outpatient monitoring, including regular endoscopic follow-up and surgical procedures in case of IBD complications [4]. In a previous study, we showed a net reduction of colonic dysplasia diagnoses and endoscopic procedures after the first COVID-19 peak in 2020 as a result of insufficient healthcare recovery [1].

As COVID-19 continued to disrupt IBD healthcare utilization and distribution during subsequent peaks, measures were taken, including telemedicine and improved triage of procedures [4,5]. However, it is unknown if these adaptations restored IBD healthcare utilization as measured by the volume of IBD procedures and diagnoses. This is especially relevant for IBD patients with delayed or missed indefinite for dysplasia (IND) and low-grade dysplasia (LGD) diagnoses since these lesions may progress to advanced neoplasia with subsequent morbidity and mortality. In addition, continued delay of endoscopic and surgical procedures might have resulted in suboptimal disease assessment and treatment.

In this nationwide study, we aimed to determine the impact of consecutive COVID-19 waves on healthcare utilization deficits, including IBD-related diagnoses and procedures during the first two years of the COVID-19 pandemic. We also assessed whether IBD healthcare utilization recovered in the second year of the pandemic.

Methods

Data source

For this nationwide retrospective cohort study, we searched the Dutch nationwide pathology databank (PALGA) [6] to identify IBD patients who underwent an IBD-related procedure between March 1, 2018, and February 28, 2022. The PALGA registry contains pseudonymized data with unique identifiers linked to individual patients and has had nationwide coverage since 1991 [6]. We repeated the PALGA search from our previously published study [1], using the same terms for IBD: 'ulcerative colitis', 'Crohn's disease', and 'chronic inflammatory bowel disease'. In addition, pathologists' report conclusions were searched using similar terms. Data

on the number of COVID-19 hospital admissions were extracted from the Dutch Patient Coordination Center (LCPS) [7].

Definitions

Procedure type (endoscopic versus surgical) was based on pathology results from either intestinal biopsy or resection specimens. IBD diagnosis was considered new in the absence of a historical pathology report. Since the first COVID-19 case in the Netherlands started on February 27, 2020, the pre-pandemic period was defined as March 2018 to February 2020, and the pandemic period was defined as March 2020 to February 2022.

Eligibility criteria

All patients with a new or existing IBD diagnosis (e.g. ulcerative colitis, Crohn's disease, and IBD-unclassified) were eligible for inclusion. Patients with a missing PALGA IBD diagnosis and the absence of IBD diagnosis in pathologists' reports were excluded from our study.

Data collection

Variables extracted from PALGA included procedure date, type, neoplasia grade (IND, LGD, HGD, or CRC), and new IBD diagnosis. We screened all individual histology records to exclude any false-positive IBD-related diagnoses.

Statistical analysis

We determined the absolute incidence of IBD-related endoscopic and surgical procedures and neoplasia diagnoses (IND, LGD, high-grade dysplasia (HGD) and colorectal cancer (CRC)) during the first and second year of the COVID-19 pandemic in the Netherlands (March 2020 – February 2021 and March 2021 – February 2022). The mean incidence of the previous two years (March 2018 – February 2020) served as a comparator. We used SPSS version 25 (IBM, Armonk, NY) to assess incidence rates. Confidence intervals and P-values were not displayed. By using complete nationwide data, we avoided sampling error when interpreting our results for the Netherlands. In regard to other countries affected by COVID-19, sampling error is likely to be small compared to major incidence influencing factors like differences in confinement measures and healthcare policies.

Ethical considerations

This study was approved by the scientific committee of PALGA (Izv-2020-123a).

Results

Our PALGA search yielded a total of 103,322 IBD-related procedures. After applying exclusion criteria, we included 89,401 (94.2%) endoscopic and 5,462 (5.8%) surgical procedures.

IBD-related procedures

We calculated a net reduction of 2.9% (1,391 IBD procedures) after the first two years of the COVID-19 pandemic compared to the two pre-pandemic years. This net reduction consists of a decrease in endoscopic procedures (-3.1%, n=1,409, figure 1), while a small increase in surgical procedures was observed (+0.7%, n=18, figure 1). We found the highest net reduction during the first peak of the pandemic in April 2020 (-59.1%, n=1166), compared to the mean incidence of April 2018 and April 2019. For both endoscopic and surgical procedures, an initial net decrease after the first pandemic year was followed by a net increase after the second year (-6.2% (n=1,413) versus +0.02% (n=4) and -1.3% (n=18) versus +2.7% (n=36), respectively).

New IBD diagnoses

A net reduction of 0.9% (n=54) in new IBD diagnoses was observed after the first two years of the COVID-19 pandemic, with a net decrease of 0.8% (n=24) and 1.0% (n=30) after the first and second pandemic year, respectively.

IBD-related neoplasia

A net reduction of 1.9% (n=74) in IND/LGD diagnoses was observed after the two-year pandemic period. We observed a net decrease of 10.9% (n=213) in IND/LGD diagnoses in the first pandemic year versus an increase of 7.1% (n=139) in the second year. No net decrease was seen for HGD and CRC diagnoses.

Discussion

In this nationwide cohort study, we found a net reduction in IBD-related procedures of approximately 3% after the first two years of the COVID-19 pandemic, including a net reduction in endoscopic procedures, new IBD diagnoses and IND/LGD diagnoses. However, no decrease in surgical procedures and HGD/CRC diagnoses was found. Importantly, we observed that IBD healthcare utilization was restored to pre-pandemic volumes in the second pandemic year.

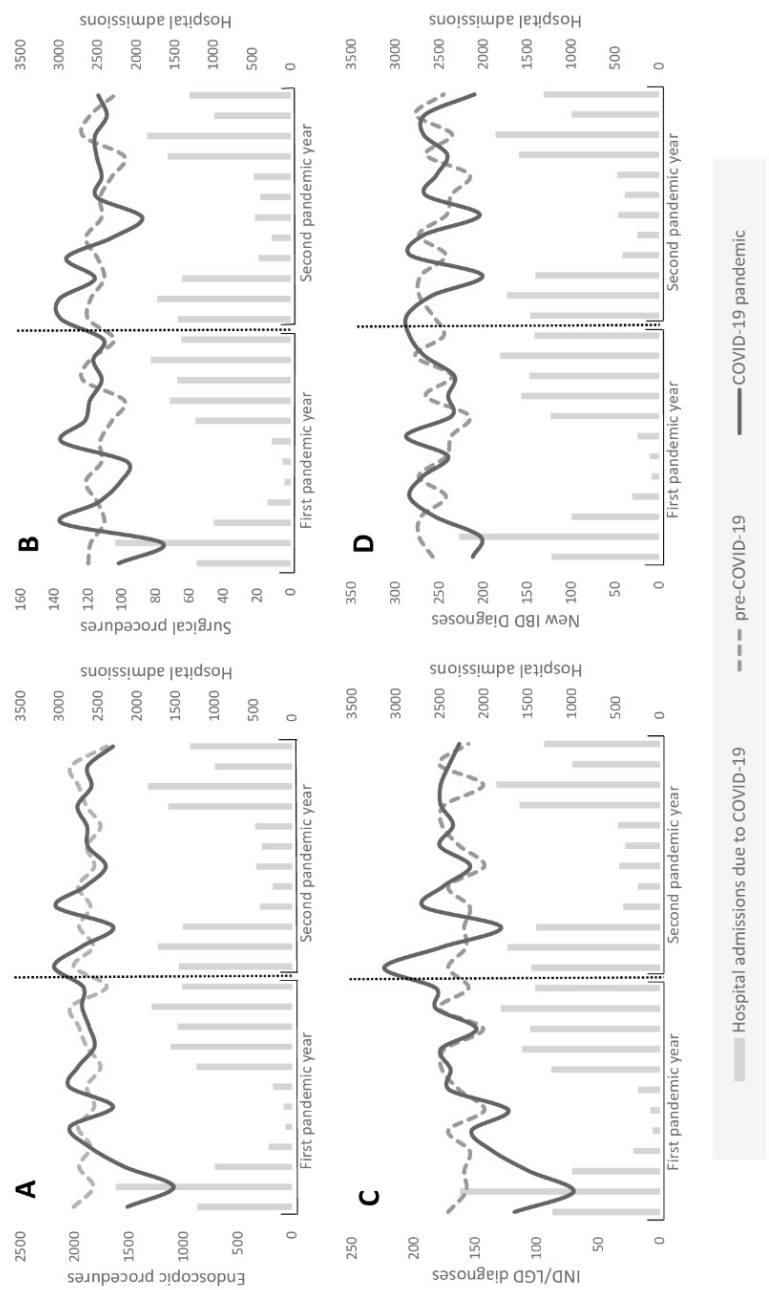

Figure 1. Total IBD-related endoscopic procedures *(A)*, surgical procedures *(B)*, indefinite and low-grade dysplasia diagnoses (IND and LGD) *(C)*, and new IBD diagnoses *(D)*. The grey bars represent the mean number of hospital beds occupied by COVID-19 patients in the Netherlands per month [7].

The net decrease of 2.9% in IBD procedures after the two-year pandemic period is most likely the result of delayed or cancelled endoscopic procedures, with even a small increase in surgical procedures (0.7%). This modest increase may result from delayed (but inevitable) surgical procedures and suboptimal treatment of inflammation or neoplasia, leading to more frequent surgical interventions.

Nearly 6 out of 10 IBD-related procedures were canceled or postponed during the first peak of COVID-19 in 2020 [1]. Our present update shows that during the subsequent COVID-19 peaks, the decline in IBD-related procedures and diagnoses was mitigated. This could be the result of more effective healthcare utilization and higher prioritization of necessary IBD healthcare [8]. In addition, improved patient education and COVID-19 vaccination strategies might have resulted in less delayed care-seeking behavior [4,9]. In line with a Dutch study showing gastroenterology procedure volumes returned to reference levels during the second wave, this trend suggests that our healthcare system is fast-adapting to overcome COVID-19 hurdles [10].

In contrast, we found a decrease in new IBD diagnoses for both pandemic years. Since the decrease was very small for both years (≤ 1%), one could hypothesize that this is a reflection of natural fluctuation in new IBD diagnoses over the years or alternatively, that changed lifestyle factors due to the pandemic impacted this reduction.

We found a decrease in IND and LGD diagnoses during the first pandemic year, with a subsequent increase in the second year. By contrast, this was not observed for HGD and CRC diagnoses. One could hypothesize that high-risk or symptomatic patients suspected of HGD or CRC receive a higher prioritization, which corroborates with previous studies that show that the initial decrease was smallest in urgent interventions [1,3,10].

Our study has several strengths. To our best knowledge, this is the first study to assess the impact of the COVID-19 pandemic during two consecutive years on IBD-related endoscopic and surgical procedures and new IBD and neoplasia diagnoses in the Netherlands. This allowed us to detect changes in procedures and IBD-related disease outcomes during the first pandemic peak and the second year of the pandemic. By using a nationwide pathology database, we were able to analyze a large cohort covering the first two years of the COVID-19 pandemic compared to incidences from the two pre-pandemic years. Limitations of our study include unavailable data on type of endoscopy (surveillance or non-surveillance) and mortality. In addition, we could not include procedures without tissue sampling since these are not available in the pathology database.

In conclusion, in this nationwide cohort study covering the first two years of the COVID-19 pandemic, we observed mitigation of the initial reduction of IBD-related procedures after the first COVID-19 wave. This finding illustrates the rapid adaptation of the national IBD healthcare system during the second year of the pandemic.

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Chapter 8

General Discussion

The aim of this thesis was to improve surveillance, diagnosis, treatment and follow-up of CRN in IBD. In this chapter I will discuss the results, strengths, limitations and clinical relevance of the studies. In addition, I will explore the remaining gaps in knowledge and propose future studies. An overview of the aims, main findings and most important limitations of each chapter is provided in table 1.

Part I: Risk stratification, surveillance and diagnosis

The aims of part I of this thesis were (1) to determine the impact of surveillance quality indicators on advanced CRN risk in IBD, and (2) to evaluate the impact of revision and expert pathologist consensus on the accuracy and prognosis of HGD in IBD.

Findings

Chapter 2 describes the impact of surveillance quality indicators on advanced CRN risk using a multicenter case-control cohort of 275 IBD patients. Our findings indicate that both prolonged intervals and active inflammation on surveillance colonoscopy increased the subsequent advanced CRN risk. Insufficient bowel preparation and incomplete procedures did not have a significant impact on the advanced CRN risk. By contrast, adhering to all quality indicators, including adequate intervals, absence of active inflammation, sufficient bowel preparation, and cecal intubation, was found to reduce the advanced CRN risk. In **Chapter 3**, we conducted a multicenter retrospective cohort study (n=54) to evaluate the impact of HGD revision and expert pathologist consensus. We found that pathologists often disagreed on lesion grade (Kappa 0.31). Following a consensus meeting, one-third of HGD diagnoses were downgraded to IND or LGD, while 10 percent was upgraded to CRC. Synchronous CRC was found in the resection specimen of 13% of patients, all of whom had either confirmed HGD or lesions upgraded to CRC. Patients whose lesions were downgraded had a significantly lower cumulative incidence of metachronous advanced CRN compared to those with confirmed advanced CRN (5-year cumulative incidence 0.0% vs 26.6%, $p < 0.01$). There were no significant differences in the cumulative incidence of metachronous CRN of any grade between the revised diagnoses.

Strengths and limitations

The strength of **Chapter 2 and 3** is the use of data from both the Dutch nationwide pathology databank (PALGA) and patient medical charts, which enabled us to collect detailed information on patient, disease, and CRN characteristics. **Chapter 2** describes the first study in IBD which primarily investigated the impact of

surveillance quality indicators on CRN risk. We calculated cumulative inflammatory burden scores for optimal confounder correction assessing the impact of active inflammation on mucosal visualization. To confirm the robustness of our data, we carried out various sensitivity analyses. There are also limitations, most importantly the retrospective design, precluding the investigation of withdrawal time and the effect of patients preferences since these were rarely reported in patient charts. In addition, the selection of IND/LGD patients as control group may limit extrapolation of our findings to IBD patients with low risk for dysplasia. Due to the retrospective design of **Chapter 3** histopathological specimens were not always available. Secondly, the metachronous CRN incidences in this study were likely influenced by the contemporary selection of HGD treatment modality, with a possible higher risk when there is more residual colon. Although we performed a competing risk analysis with proctocolectomy as competing event, we did not apply confounder correction for the selected treatment modality otherwise.

Clinical implications

The findings in **Chapter 2** substantiate current guideline recommendations. The impact of active colonic inflammation on advanced CRN risk, even after correction for cumulative inflammatory burden, highlights the recommendation to perform surveillance during disease remission to ensure optimal mucosal visualization. However, disease remission can be difficult to achieve in patients with severe IBD phenotypes like some cases in our study. Delayed surveillance intervals, with a median 26 months delay, were associated with advanced CRN, underlining the need for stringent interval adherence. The substantial inter-observer variability found in **Chapter 3** is aligned with previous studies and highlights the challenge of accurately diagnosing HGD, even for expert pathologists [1-3]. The frequently downgraded CRN diagnoses with corresponding adjustment of prognosis suggest the potential of expert pathologist consensus meetings. Implementing such meetings in clinical practice may prevent over- and undertreatment of CRN in IBD, and thus may prevent unnecessary colectomies and preserve bowel function, and vice versa, may also prevent frequent colonoscopies in selected patients. However, we recognize that the feasibility of establishing expert panels may vary depending on the political and financial circumstances in different regions.

Gaps in knowledge and future studies

Chapter 2 lays the groundwork for future research on new quality indicators in IBD. Established quality indicators in the non-IBD surveillance population, such as adenoma detection rate (ADR) and withdrawal time, have a known correlation with interval CRC[4]. Nonetheless, their relevance in the IBD population remains unclear.

In our study, cut-off values for surveillance intervals were based on current expert-based guideline recommendations[5]. It is uncertain if the recommended one, three, or five yearly intervals result in optimal CRC risk reduction. Larger prospective cohort studies may compare different intervals to address this important gap in knowledge, since randomized clinical trials are not feasible due to ethical, financial and time constraints.

Mucosal visualization is another important factor that impacts timely CRN detection. The debate on the adequate visualizing technique in IBD is ongoing. The use of high-definition equipment and enhanced image endoscopy (e.g. DCE and VCE)[6] aids in visualizing most lesions that were previously characterized as invisible.. Although there is consensus on the added value of DCE compared to standard definition white light endoscopy, some debate remains on its position compared to high definition white light endoscopy [7-9]. Since DCE results in longer procedural times, higher costs and reduced visualization in case of inflammation and suboptimal bowel preparation, high-definition white light endoscopy is often favored in clinical practice, which explains the low DCE rate in our study [10]. A recent randomized controlled trial showed that high-definition white light endoscopy with segmental re-inspection was non-inferior compared to DCE for CRN detection in IBD [11]. In addition, recent studies show promising results for the added value of artificial intelligence (AI) on lesion detection in the general population [12,13]. Future studies may focus on AI to improve lesion detection in the IBD population.

Other factors that may negatively impact mucosal visualization are active inflammation and a high density of post-inflammatory polyps [14]. Hence, future studies may focus on short-term strategies for disease remission prior to surveillance, with rapid-acting anti-inflammatory drugs such as corticosteroids and Janus kinase inhibitors. In addition, the standard use of non-targeted biopsies is no longer recommended by guidelines when using enhanced image techniques, since their neoplastic yield is negligible, although it might be of added value when mucosal visualization is impaired or in patients with high CRN risk [15-18]. A recent study showed that the neoplastic yield of non-targeted biopsies is increased in patients with active colonic inflammation [19].

Lastly, future studies and clinical pathways should focus on improving guideline adherence. Physician adherence could be improved by digital decision aids for risk stratification and automated reminders to ensure timely surveillance endoscopy. On the other hand, shared decision making, with appreciation of patient preferences is key to improve patient adherence. To achieve this, patients should be properly

educated on CRC risk, and burden and benefits of surveillance.. Prospective studies should evaluate the impact of these measures on surveillance participation, guideline adherence, and ultimately development of CRN.

Chapter 3 is an example of a measure to improve accuracy of histopathological CRN diagnosis in IBD. Future studies might research the impact of centralization and pathologist training on diagnostic accuracy and prognosis of CRN, as these measures showed potential in Barrett's esophagus surveillance. Prior studies in Barrett's esophagus showed frequent downgrading after expert pathologist review, although after structured assessment and group discussions, pathologists are homogeneous in their review of biopsies of LGD in Barrett's esophagus [20,21]. Also, the role of pathologists in multidisciplinary teams should be explored, especially in complex CRN cases. The relative low rate of CRN in IBD makes it harder to gain diagnostic experience for both gastroenterologists and pathologists. Therefore, specific training should be a priority, for example with an easily accessible online training module [22]. In addition, artificial intelligence systems show promise for supporting physicians in CRN detection and diagnosis in the non-IBD population [23-25]. However, its use in the IBD population requires further investigation, along with the establishment of repositories comprising endoscopic videos and histological slides of CRN in IBD, for adequate training of AI systems [26].

Part II: Treatment and follow-up

The aims of part II of this thesis were (1) to compare the synchronous and metachronous CRN risk after endoscopic resection, partial colectomy and (sub) total colectomy for advanced CRN in IBD, and (2) determine the long-term risk of CRC after HGD diagnosis in IBD.

Findings

Chapter 4 describes a multicenter retrospective cohort study comparing the synchronous and metachronous CRN risk following endoscopic resection, partial colectomy and (sub)total colectomy in IBD patients with advanced CRN, including HGD and CRC (n=189). Synchronous and metachronous CRN was detected in one-fourth and one-third of patients, respectively. We found a comparable metachronous CRN risk after partial colectomy and (sub)total colectomy. This underlines the consideration of partial colectomy as a treatment strategy for patients with limited disease extent without other CRC risk factors. In contrast, endoscopic resection resulted in a significantly higher risk of metachronous CRN, compared to (sub)

total colectomy. All-cause mortality after CRC did not differ between treatment modalities. Limited disease extent and older age were associated with a treatment choice for partial colectomy and endoscopic resection. In **Chapter 5** we performed a nationwide retrospective cohort study to assess the risk of CRC after a diagnosis of HGD in 1,223 IBD patients. One out of six patients had synchronous CRC after initial HGD diagnosis. The 10-year cumulative incidence of metachronous CRC was 17.2%. Post-inflammatory polyps, academic origin of pathology report and endoscopic treatment of HGD were associated with metachronous CRC. We found an increased proportion of surgical treatment of index HGD over time.

Strengths and limitations

The strength of **Chapter 4** is use of PALGA, the Dutch nationwide pathology databank, combined with data from patient medical charts. This enabled us to collect detailed information on patient, disease, and CRN characteristics. In addition, we performed a competing risk analysis to reduce overestimation of metachronous CRN due to proctocolectomy or death during follow-up. There are also limitations to address. Due to the limited number of metachronous advanced CRN we were not able to assess independent associations. In addition, patient and physician preferences have likely influenced treatment choice. For example, comorbidities, fear of an ostomy, or underlying IBD severity may have impacted this decision. Unfortunately, patients charts rarely addressed these preferences upon review. **Chapter 5** has several strengths, most importantly the nationwide design allowing us to build the largest world-wide HGD cohort in IBD to date. In addition, our time-frame analyses enabled us to assess possible change in metachronous CRC risk over time. Limitations include incomplete data on IBD duration, which we attempted to overcome with data imputation. Moreover, data on IBD extent and severity were not available in PALGA, hampering estimation of the historic inflammatory burden per patient.

Clinical implications

The similar metachronous CRN rates found after partial colectomy and (sub) total colectomy in **Chapter 4** underline the feasibility of partial colectomy for a selected group of IBD patient with limited disease extent without other CRC risk factors. On the other hand, the high metachronous CRN and CRC rates after endoscopic resection found in both **Chapter 4 and 5** suggest that this treatment modality should only be considered if a lesion is endoscopically resectable and subsequent stringent endoscopic surveillance is feasible without impairment of mucosal visualization due to, for example, active inflammation, strictures or post inflammatory polyps. Of note, a tailored treatment strategy is recommended where age, comorbidity and individual CRC risk should be taken into account. Moreover,

the high risk of CRC within 6 months after HGD diagnosis that was found in **Chapter 5** indicates both the need for clinical awareness and careful endoscopic assessment after HGD diagnosis, as well as the risk of sampling error and the challenging histopathological differentiation between HGD and CRC in IBD. The findings of these studies facilitate further CRC risk classification of this subgroup of IBD patients and may subsequently aid in selecting the appropriate treatment strategy for HGD, where the advantage of endoscopic resection, including prevention of bowel surgery and preserving bowel function, should be balanced with the higher risk of metachronous CRC. Treatment selection warrants a multidisciplinary approach including gastroenterology, pathology and surgery teams.

Gaps in knowledge and future studies

Chapter 4 and 5 are examples of two of the largest advanced CRN and HGD cohorts in IBD to date. Most recommendations in CRN management and post-resection surveillance in IBD patients are based on low quality evidence and expert opinions, since large prospective studies are lacking [5,15,27,28]. Ideally, gastroenterologists and surgeons apply personalized surveillance and treatment strategies, based on individualized predicted CRN risk and patient preferences. In order to provide this, there is a need for high-quality data on the exact magnitude of the synchronous and metachronous CRN risk following different endoscopic surveillance techniques, intervals and treatment modalities, and the impact of specific IBD and CRN characteristics. However, IBD study designs and methodology are limited by the low and decreasing incidence of (advanced) CRN, and the required long follow-up time to detect these events. These limitations are significant hurdles that make the design of randomized controlled and prospective trials very challenging. Hence, future studies should focus on collaboration between high volume centers preferably from different continents, to provide more large scale, prospective data with external validity. As such, we are currently collaborating with colleagues from Edmonton (Canada) and Chicago (the United States of America) to perform a case-control study to assess the impact of chronic active inflammation per colonic segment on the CRN risk in PSC-IBD patients. Patients with IBD and concomitant PSC have a 5-20 times higher CRC risk compared to IBD patients without PSC and are therefore subjected to the highest risk category of CRC with mandated annual endoscopic surveillance [29,30]. A better understanding of the CRN risk profile of PSC-IBD patients may improve surveillance and treatment strategies. We expect to finish data analyses at the end of 2024.

Part III: Healthcare utilization

The aims of part III of this thesis were (1) to determine the decrease in delivered IBD healthcare during the first part of the COVID-19 pandemic in the Netherlands, and (2) to provide a 2-year nationwide update, assessing the impact of consecutive COVID-19 waves on IBD healthcare utilization. We specifically focused on endoscopic surveillance in IBD patients.

Findings

In **Chapter 6** we performed a nationwide retrospective cohort study that showed a large reduction in IBD healthcare during the COVID-19 pandemic in 2020 in the Netherlands. We found a reduction in total incidence of IBD-related endoscopic and surgical procedures, new IBD diagnoses and IND/LGD diagnoses. At the peak of the first wave of the pandemic in April 2020, almost 6 out of 10 procedures were canceled or postponed. Despite a relative increase in the subsequent months, an overall reduction of 14.2% remained at the end of follow-up. No reduction was observed for HGD or CRC diagnoses. **Chapter 7** describes a two-year nationwide update with a modest net reduction in IBD-related procedures of 3%, including endoscopic procedures, new IBD diagnoses, and IND/LGD diagnoses. No decrease in surgical procedures and HGD/CRC diagnoses was found. Of note, IBD healthcare utilization was restored to pre-pandemic volumes in the second pandemic year.

Strengths and limitations

A strength of **Chapter 6 and 7** is the use of the nationwide PALGA database allowing us to analyze a large cohort. In addition, **Chapter 7** is the first study to assess the impact of the COVID-19 pandemic during 2 consecutive years on IBD-related healthcare. Limitations of **Chapter 6 and 7** include the lack of data on type of endoscopy (surveillance or non-surveillance) and mortality. Moreover, procedures without tissue sampling could not be included, since these are not recorded in the pathology database.

Clinical implications

The incomplete recovery of missed procedures and diagnoses after the first COVID-19 wave in **Chapter 6** implies the need for optimization of healthcare systems to prevent negative outcomes. Fortunately, the mitigation of the decline after two pandemic years in **Chapter 7** suggests that our healthcare system is fast adapting to overcome COVID-19 hurdles. This could be the result of better prioritization of IBD healthcare, improved patient education and vaccination strategies resulting in less delayed care-seeking behavior. These data may aid

healthcare providers and policy makers during potential future pandemics, but also provide direction in times of significant budget restraints for healthcare systems.

Gaps in knowledge and future studies

The true clinical impact of the COVID-19 pandemic on cancelled and postponed IBD procedures could be measured in IBD and CRC related morbidity and mortality. For example, one study showed that a 3-month delay in cancer surgery reduced the benefit in life-years gained of all COVID-19 care by 19% [31]. **Chapter 6 and 7** provide a foundation for a follow-up study with an even wider timeframe and linkage with the national cancer registry of the Netherlands (NCR), allowing assessment of IBD and CRC related morbidity and mortality after the COVID-19 pandemic.

Conclusion

This thesis aimed to improve surveillance, diagnosis, treatment and follow-up of CRN in IBD. Adherence to guideline recommendations and surveillance is essential for effective surveillance and to improve clinical outcomes. Expert pathologist consensus for HGD may aid in improving diagnostic and prognostic accuracy, preventing misdiagnoses with subsequent under- and overtreatment. Advances in endoscopic resection techniques and endoscopic surveillance have expanded non-surgical treatment options for CRN in IBD. Despite this progress, the high risk of synchronous and metachronous CRN after endoscopic resection warrants an intensified endoscopic surveillance after CRN resection in case of residual colon. The COVID-19 pandemic resulted in a significant decrease in IBD healthcare, with a concerning decline in IND/LGD diagnosis, while the impact on morbidity and mortality have not yet been studied.

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Table 1. Summary of main findings of this thesis

Chapter	Aim(s)	Main findings and conclusion	Limitation and comments
Part I: Risk stratification, surveillance and diagnosis			
2	• To determine the impact of quality indicators on advanced CRN risk in IBD	• Delayed intervals and presence of active inflammation were associated with an increased advanced CRN risk • High-quality surveillance was associated with a reduced advanced CRN risk • **Adherence to guideline recommendations and surveillance during disease remission are essential for effective surveillance**	• Retrospective cohort with inherent biases such as selection bias • Control group with IND/LGD patients
3	• To evaluate the inter-observer variability and the impact of expert pathologist consensus on the prognosis of HGD in IBD	• The inter-observer agreement was 'fair' (Kappa 0.31) • The 33.3% of lesions that were downgraded after expert pathologist consensus had a significantly lower metachronous advanced CRN rate • Confirmation of HGD diagnosis or an upgrade to CRC (11.1%) resulted in a higher metachronous advanced CRN rate. • **Expert pathologist consensus improves the accuracy of HGD diagnosis and prognosis**	• Retrospective cohort with inherent biases such as selection bias • No adjustment for treatment modality
Part II: Treatment and follow-up			
4	• To compare synchronous and metachronous (advanced) CRN rates following endoscopic resection, partial colectomy or (sub) total colectomy for advanced CRN, including impact of IBD type • To determine the impact of treatment modalities on all-cause mortality • To determine associations with treatment choice	• Synchronous and metachronous CRN was detected in one-fourth and one-third of patients, respectively • CRN risks after partial colectomy and (sub)total colectomy were comparable • Endoscopic resection resulted in a significantly higher risk of metachronous CRN • **Partial colectomy may be considered in patients with limited disease extent without other risk factors**	• Retrospective cohort with inherent bias such as selection bias • Small sample size with limited number of metachronous advanced CRN

Table 1. Continued

Chapter	Aim(s)	Main findings and conclusion	Limitation and comments
5	• To determine the long-term risk of CRC and CRN after HGD diagnosis in IBD • To identify risk factors for metachronous CRC and CRN • To provide trends in choice of treatment strategies over the past three decades	• Within 6 months after HGD diagnosis, 1 of 6 patients was diagnosed with (synchronous) CRC • The 10-year cumulative incidence of metachronous CRC and CRN were 15.9% and 75.2%, respectively • There was no increased proportion of endoscopic treatment over time • **The colon sparing advantage of endoscopic resection of HGD should be balanced with the metachronous CRC risk and the subsequent need for stringent endoscopic surveillance**	• Incomplete data on IBD duration, for which we performed data imputation • No available data on IBD extent and severity in PALGA, limiting estimation of historic inflammatory burden per patient • Possible underestimation of presence of PIPs, PSC and strictures
Part III: Healthcare utilization			
6	• To determine the decrease in delivered IBD healthcare during the COVID-19 pandemic	• Endoscopic and surgical procedures showed a net decrease of 14.7% • New IBD diagnoses during the COVID-19 pandemic decreased by 6.5% • IND/LGD diagnoses decreased by 25.5%, but there was no decrease in HGD/CRC diagnoses • **The COVID-19 pandemic resulted in a significant decrease in IBD healthcare, with a concerning decline in IND/LGD diagnoses**	• No clinical data from patient charts available • No data on procedures without histopathological tissue sampling
7	• To determine the impact of consecutive COVID-19 waves on healthcare utilization during the first 2 years of the COVID-19 pandemic	• Endoscopic and surgical procedures showed a net decrease of 2.9% • IND/LGD diagnoses decreased with 10.9% in the first pandemic year and increased with 7.1% in the second year • No decrease was observed in HGD/CRC diagnoses • **The initial reduction in IBD-related procedures was mitigated after the first 2 years of the COVID-19 pandemic**	• No mortality data available • No data on procedures without histopathological tissue sampling

Appendices

Summary
Dutch summary (Nederlandstalige samenvatting)
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Summary

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract, and includes Crohn's disease (CD) and ulcerative colitis (UC). IBD is characterized by relapsing symptoms of abdominal pain, diarrhea, rectal blood loss, urgency, weight loss and fatigue. IBD is usually treated with a wide range of anti-inflammatory medication and colorectal surgery to control disease activity and to prevent or treat complications such as strictures, fistulae, abscesses and colorectal neoplasia (CRN). As a result of chronic active inflammation, IBD patients are at increased risk of developing CRN as compared to the general population. CRN naturally progresses through various stages from low-grade dysplasia (LGD) to high-grade dysplasia (HGD) to colorectal cancer (CRC). HGD and CRC are considered advanced neoplasia. Endoscopic surveillance is recommended by international guidelines in order to detect and remove CRN at an early stage. Patients are stratified to a low-, intermediate- and high-CRC risk category, corresponding with a surveillance interval of 5, 3 and 1 year, respectively. If an advanced CRN would be diagnosed, historically a colectomy was recommended. However, recent advances in endoscopic surveillance and resection techniques have facilitated a shift towards an endoscopic treatment strategy. Many gaps in knowledge remain to further optimize evidence-based recommendations on the optimal CRN surveillance technique and interval, CRN management and endoscopic follow-up strategy. The overarching aim of this thesis was to evaluate and improve surveillance and management of CRN in IBD.

In **part I** we evaluated the value of quality indicators of endoscopic surveillance in IBD and expert pathologist revision and consensus for HGD diagnosis.

In **chapter 2**, we performed a multicenter case-control study to assess multiple quality indicators recommended by guidelines, including surveillance interval, disease remission, cecal intubation, and bowel preparation. We found that delayed endoscopy intervals and presence of active inflammation were associated with advanced CRN. Hence adherence to guideline recommendations, and surveillance during disease remission are essential for more effective surveillance.

Chapter 3 evaluates the impact of expert pathologist consensus of HGD diagnosis in IBD. We found that after a consensus meeting, 1 of 3 HGD diagnoses were downgraded. Confirmation of HGD diagnosis or an upgrade to CRC resulted in a higher metachronous advanced CRN rate, compared to downgrading. This emphasizes the need for expert pathologist consensus meeting to prevent over- and undertreatment of HGD in IBD.

Part II focused on CRN treatment and follow-up.

In **chapter 4** we compared synchronous and metachronous CRN rates following different treatment strategies for HGD and CRC, including endoscopic resection, partial colectomy and (sub)total or proctocolectomy. Partial colectomy resulted in long-term CRN risks comparable to (sub)total colectomy, underlining the potential of this treatment strategy for a subgroup of IBD patients with limited disease extent without other CRN risk factors. Endoscopic resection was associated with a higher risk of metachronous CRN, warranting continued stringent post-polypectomy endoscopic surveillance.

Chapter 5 describes a nationwide study to determine the long-term risk of CRC after HGD diagnosis and to provide trends in selection of HGD treatment over the past three decades. After 10 year of follow-up 15.9% of patients developed metachronous CRC and endoscopic treatment (versus surgery) was associated with a higher risk of metachronous CRC. The advantages of colon sparing treatment should be carefully balanced with the higher metachronous CRC risk and the subsequent need for stringent endoscopic surveillance.

In **part III** we determined IBD healthcare utilization during the COVID-19 pandemic.

In **chapter 6** we determined the decrease in delivered IBD healthcare in the Netherlands during the first COVID-19 wave. We found a net decrease of 14.7% in endoscopic and surgical IBD procedures. Even more concerning was the observed 25.5% decline in non-advanced CRN diagnoses. However, there was no decrease in HGD and CRC diagnoses. These findings imply that there is a need for optimization and better prioritization of IBD healthcare systems to prevent negative outcomes.

Chapter 7 provides a two-year nationwide update of the study described in chapter 6, which shows that the initial reduction in IBD-related procedures was mitigated after the first 2 years of the COVID-19 pandemic, illustrating the rapid adaptation of the national IBD healthcare system. Combined, both chapters may aid healthcare providers and policy makers during potential future pandemics or times of budget restraints.

To conclude, this thesis aimed to improve surveillance, diagnosis, treatment and follow-up of CRN in IBD. Adherence to quality indicators recommended by guidelines is essential for effective surveillance, while an expert pathologist consensus meeting may prevent over- and undertreatment of HGD in IBD. In

terms of treatment, partial colectomy could be a feasible alternative for (sub) total or proctocolectomy in selected IBD patients with HGD or CRC. The high risk of CRN and CRC after endoscopic resection warrants an intensified endoscopic surveillance after CRN resection in case of residual colon. Finally, the COVID-19 pandemic resulted in a significant decrease in IBD healthcare, with a concerning decline in non-advanced CRN, while the impact on morbidity and mortality have not yet been studied.

Nederlandstalige samenvatting

Inflammatoire darmziekte (IBD) is een chronische ontstekingsziekte van het maag-darmkanaal. Hieronder vallen de ziekte van Crohn (CD) en colitis ulcerosa (UC). IBD wordt gekenmerkt door terugkerende symptomen van buikpijn, diarree, rectaal bloedverlies, aandrang, gewichtsverlies en vermoeidheid. IBD wordt gewoonlijk behandeld met een breed arsenaal aan ontstekingsremmende medicatie en chirurgische darmresectie. Het doel van die behandeling is het onder controle brengen van de ziekteactiviteit, om zo ook complicaties zoals vernauwingen, fistels, abcessen en colorectale neoplasie (CRN) te voorkomen of te behandelen. Patiënten met IBD hebben, als gevolg van chronische actieve inflammatie, een verhoogd risico op CRN vergeleken met de algemene bevolking. CRN ontwikkelt zich geleidelijk via verschillende stadia van laaggradige dysplasie (LGD) naar hooggradige dysplasie (HGD) tot darmkanker (CRC). HGD en CRC worden beschouwd als gevorderde neoplasie. Endoscopische surveillance wordt aanbevolen door internationale richtlijnen, waarmee CRN vroegtijdig kan worden opgespoord en verwijderd. Patiënten worden ingedeeld in een laag- middel- of hoog-risico groep, wat correspondeert met een surveillance interval van respectievelijk 5, 3 of 1 jaar. Vroeger werd een chirurgische darmresectie geadviseerd in het geval van een gevorderde CRN diagnose. Echter recente ontwikkelingen in endoscopische surveillance en resectie technieken hebben mogelijk gezorgd voor een verschuiving naar een endoscopische behandelstrategie. Er zijn veel resterende kennishiaten die zorgen voor belemmering in het optimaliseren van wetenschappelijk bewezen aanbevelingen voor surveillance techniek en interval, behandeling en endoscopische follow-up in geval van CRN in IBD patiënten. Het algehele doel van dit proefschrift was het evalueren en verbeteren van surveillance en behandeling van CRN in IBD.

In **deel I** hebben we de waarde van kwaliteitsindicatoren van endoscopische surveillance in IBD en revisie en consensus door expert pathologen geëvalueerd.

In **hoofdstuk 2** hebben we een multicenter case-control studie verricht om meerdere kwaliteitsindicatoren te onderzoeken die aanbevolen worden door richtlijnen, zoals surveillance interval, ziekteremissie, coecumintubatie en darmvoorbereiding. Uit de studie bleek dat een verlengd surveillance endoscopie interval en ziekteactiviteit tijdens surveillance geassocieerd waren met gevorderde CRN. Hieruit maken wij op dat voor meer effectieve surveillance het essentieel is dat men zich houdt aan de aanbevelingen uit de richtlijnen en dat men surveillance uitvoert tijdens ziekteremissie.

Hoofdstuk 3 evalueert de impact van expert patholoog consensus over HGD diagnose in IBD. Na een consensus meeting werd 1 op de 3 HGD diagnoses afgezwakt naar een lagere gradering. Wanneer een HGD diagnose werd bevestigd of als CRC werd beschouwd, leidde dat tot een hoger risico op metachrone gevorderde CRN. Deze bevindingen benadrukken het nut van expert patholoog consensus besprekingen ter voorkoming van over- en onderbehandeling van HGD in IBD.

In **deel II** leggen we de focus op CRN behandeling en follow-up.

In **hoofdstuk 4** vergelijken we synchrone en metachrone CRN risico's na verschillende behandelstrategieën voor HGD en CRC. Hieronder vallen endoscopische resectie, gedeeltelijke chirurgische darmresectie en (bijna) volledige chirurgische darmresectie. Gedeeltelijke en (bijna) volledige chirurgische darmresectie leidde tot vergelijkbare lange-termijn CRN risico's, hetgeen de potentie van deze behandelstrategie onderstreept voor een subgroep van IBD patiënten met beperkte ziekte uitbreiding zonder andere CRN risicofactoren. Endoscopische resectie daarentegen was geassocieerd met een hoger risico op metachrone CRN, waardoor strikte endoscopische surveillance na poliepverwijdering gehandhaafd dient te worden.

Hoofdstuk 5 beschrijft een nationale studie ter bepaling van het lange-termijn risico op CRC na HGD diagnose en ter inzage in trends in HGD behandelkeuze in de afgelopen drie decennia. Na 10 jaar follow-up na HGD bleek 15,9% van de patiënten metachrone CRC te hebben ontwikkeld, waarbij endoscopische behandeling (vs chirurgie) geassocieerd bleek met een hoger risico op metachrone CRC. De voordelen van darmsparende behandeling moeten derhalve voorzichtig worden afgewogen tegen het hogere metachrone CRC risico en de bijbehorende noodzaak tot strikte endoscopische surveillance.

In **part III** bepaalden we het gebruik van IBD gezondheidszorg tijdens de COVID-19 pandemie.

In **hoofdstuk 6** bepaalden we het verschil in geleverde IBD zorg in Nederland tijdens de eerste COVID-19 golf. Hierbij vonden we een netto reductie van 14,7% in endoscopische en chirurgische IBD procedures. Verontrustender was de geobserveerde daling van 25,5% in niet-gevorderde CRN diagnoses. Echter werd geen verlies gevonden in HGD en CRC diagnoses. Deze bevindingen onderstrepen

de noodzaak voor optimalisatie en betere prioritering van IBD gezondheidszorg systemen ter voorkoming van nadelige uitkomsten.

Hoofdstuk 7 geeft een twee-jaar nationale update van de studie omschreven in hoofdstuk 6, waarbij de initiële reductie in IBD-gerelateerde procedures bleek te zijn verholpen na de eerste twee jaar van de COVID-19 pandemie. Dit illustreert het snelle aanpassingsvermogen van de nationale IBD zorg systemen. Beide hoofdstukken samen kunnen van nut zijn voor zorgaanbieders en beleidsmakers tijdens potentiële toekomstige pandemieën of in tijden van bezuinigen in de gezondheidszorg.

Concluderend, dit proefschrift had als doel het verbeteren van CRN surveillance, diagnose, behandeling en follow-up in IBD. Het naleven van kwaliteitsindicatoren voor surveillance die worden geadviseerd door richtlijnen is essentieel voor een effectieve surveillance. Expert patholoog consensus bijeenkomsten kunnen mogelijk over- en onderbehandeling van HGD in IBD voorkomen. In termen van behandeling kan gedeeltelijke chirurgische darmresectie dienen als alternatief voor (bijna) volledige darmresectie in een specifieke groep IBD patiënten met HGD en CRC. Het hoge risico van CRN en CRC na endoscopische resectie vraagt om aangescherpte endoscopische surveillance na CRN resectie zo lang er nog darm in het lichaam achterblijft. Tot slot heeft de COVID-19 pandemie geleid tot een significante reductie in IBD zorg, met een verontrustende daling in niet-gevorderde CRN diagnoses. De echte impact hiervan op morbiditeit en mortaliteit is nog niet onderzocht.

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About the author

Nederlands

Monica Eduarda Wilhelmina Derks werd geboren op 25 januari 1994 te Mill. Zij groeide op in Mill, te midden van haar ouders Eddy en Thea en haar oudere zus Manon. In 2012 behaalde zij haar VWO diploma aan het Udens College. Na een succesvolle decentrale selectie startte zij datzelfde jaar met de opleiding Geneeskunde aan het Radboudumc te Nijmegen. Niet veel later ontmoette zij Hans met wie zij twee jaar later ging samenwonen.

In 2015 behaalde zij haar bachelor Geneeskunde. In haar wachttijd reisde zij door Azië en deed onder andere vrijwilligerswerk in Nepal, bestaande uit educatie over hygiëne en infectiepreventie. Tijdens de masterfase van haar studie werd haar interesse voor de Maag-, Darm- en Leverziekten gewekt, waarop zij een klinische stage volgde bij de Maag-, Darm- en Leverziekten in het Bernhoven Ziekenhuis. Ze deed haar wetenschappelijke stage naar de opsporing van poliepen en darmkanker met behulp van een elektronische neus, onder begeleiding van Kelly van Keulen en prof. P.D. Siersema.

Na het behalen van haar artsenbul in 2019 werkte zij als arts-assistent niet in opleiding bij de Interne Geneeskunde in het Canisius Wilhelmina Ziekenhuis te Nijmegen. Een jaar later, ten tijde van de COVID-19 pandemie, begon zij haar promotietraject over darmkanker surveillance in patiënten met inflammatoire darmziekten aan het Radboudumc, onder begeleiding van prof. dr. F. Hoentjen, prof. dr. J.P.H. Drenth en dr. M te Groen. Deze functie combineerde zij ruim twee jaar met een functie als trialarts. In 2023 werd dochter Lena geboren. De laatste maanden van haar promotietraject was Monica tevens werkzaam als arts-assistent niet in opleiding bij de Maag-, Darm- en Leverziekten in het Radboudumc te Nijmegen. In 2024 ronde zij haar promotietraject af. Vanaf 2025 werkt Monica als arts-assistent niet in opleiding bij de Maag-, Darm- en Leverziekten in het Catharina Ziekenhuis te Eindhoven.

English

Monica Eduarda Wilhelmina Derks was born on January 25, 1994, in Mill. She grew up in Mill, surrounded by her parents, Eddy and Thea, and her older sister, Manon. In 2012, she obtained her VWO diploma at Udens College. Following a successful decentralized selection process, she began her study in Medicine at Radboudumc in Nijmegen that same year. Shortly thereafter, she met Hans, with whom she moved in two years later.

In 2015, she earned her bachelor's degree in Medicine. During her gap period, she traveled through Asia, engaging in activities such as volunteering in Nepal, which involved educating on hygiene and infection prevention. During the master's phase of her study, her interest in Gastroenterology and Hepatology was sparked, leading her to undertake a clinical internship in Gastroenterology and Hepatology at Bernhoven Hospital. She conducted her scientific internship on the detection of polyps and colorectal cancer using an electronic nose, under the supervision of Kelly van Keulen and Prof. P.D. Siersema.

After earning her medical degree in 2019, she worked as a junior doctor in Internal Medicine at Canisius Wilhelmina Hospital in Nijmegen. A year later, during the COVID-19 pandemic, she began her PhD research on colorectal cancer surveillance in patients with inflammatory bowel diseases at Radboudumc, under the supervision of Prof. Dr. F. Hoentjen, Prof. Dr. J.P.H. Drenth, and Dr. M. te Groen. She combined this role for more than two years with a position as a trial physician. In 2023, her daughter Lena was born. In the final months of her PhD trajectory, Monica also worked as a junior doctor in Gastroenterology and Hepatology at Radboudumc in Nijmegen. In 2024, she completed her PhD. From January 2025 on, Monica works as a junior doctor in Gastroenterology and Hepatology at Catharina Hospital in Eindhoven.

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List of publications

Reduction in inflammatory bowel disease healthcare during the coronavirus disease 2019 pandemic: a nationwide retrospective cohort study
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Inflammatory Bowel Diseases, 2024, p. 146-149, DOI: 10.1093/ibd/izad055

Management of colorectal neoplasia in IBD patients: current practice and future perspectives

Monica E.W. Derks, Maarten te Groen, Lisa M.A. van Lierop, Sanjay Murthy, David T. Rubin, Talat Bessissow, Iris D. Nagtegaal, Willem A. Bemelman, Lauranne A.A.P. Derikx, Frank Hoentjen

Journal of Crohns and Colitis, 2024, ePub, DOI: 10.1093/ecco-jcc/jjae071

Revision and expert pathologist consensus of high-grade dysplasia in IBD impacts the advanced neoplasia rate: a multicenter study

Maarten te Groen, Monica E.W. Derks, Iris D. Nagtegaal, Charlotte P. Peters, Annemarie C. de Vries, Gerard Dijkstra, Tessa E.H. Romkens, Carmen S. Horjus, Nanne K. de Boer, Michiel E. de Jong, Britt van Ruijven, Frank Hoentjen, Shoko Vos, Lauranne A.A.P. Derikx

Submitted

High risk of colorectal cancer after high-grade dysplasia in inflammatory bowel disease patients

Monica E.W. Derks, Maarten te Groen, Lauranne A.A.P. Derikx, Iris D. Nagtegaal, Frank Hoentjen

Submitted

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Research data management

Ethics and privacy

This thesis is based on the results of research involving human participants, which were conducted in accordance with relevant national and international legislation and regulations, guidelines, codes of conduct and Radboudumc policy. The institutional ethical review committees CMO Radboudumc, Nijmegen, the Netherlands (file numbers: 2017-3219 and 2024-17445) and the PALGA scientific committee (file numbers: lzv2019-87, lzv2022-80, lzv2020-123 and lzv2020-123a) have given approval to conduct these studies.

According to Dutch legislation, data collection from electronic patient files was performed by personnel with a treatment relationship with the patient. The privacy of the participants in these studies was warranted by the use of pseudonymization. The pseudonymization key was stored on a secured network drive that was only accessible to members of the project who needed access to it because of their role within the project. The pseudonymization key was stored separately from the research data.

Data collection and storage

Data for all chapters was obtained through PALGA, the Dutch nationwide pathology databank. Additional data from electronic patients files for chapter 2, 3 and 4 were collected through an electronic Case Report Forms (eCRF) using Castor EDC (Amsterdam, the Netherlands). Additional data for chapter 7 was obtained through the national cancer registry of the Netherlands (NCR or IKNL). Data were converged to SPSS (IBM, Armonk, NY, USA) and R statistical software. Pseudonymized data were stored on departments server and in Castor EDC and are only accessible by project members. To ensure interpretability of the data, filenames, primary and secondary data, metadata, descriptive files and program codes and scripts are documented along with the data.

Availability of data

All studies are published open access. The data will be archived for 15 years after termination of the study. While permission for data sharing was not obtained, the data are archived in a 'closed access' Data Acquisition Collection (DAC) of the Radboud Data Repository, from which the metadata are publicly available via DOI: 10.34973/r6sm-g588 (chapter 2), 10.34973/f6xd-5s52 (chapter 4), 10.34973/gq0f-km25 (chapter 6), and 10.34973/b12c-m367 (chapter 7).

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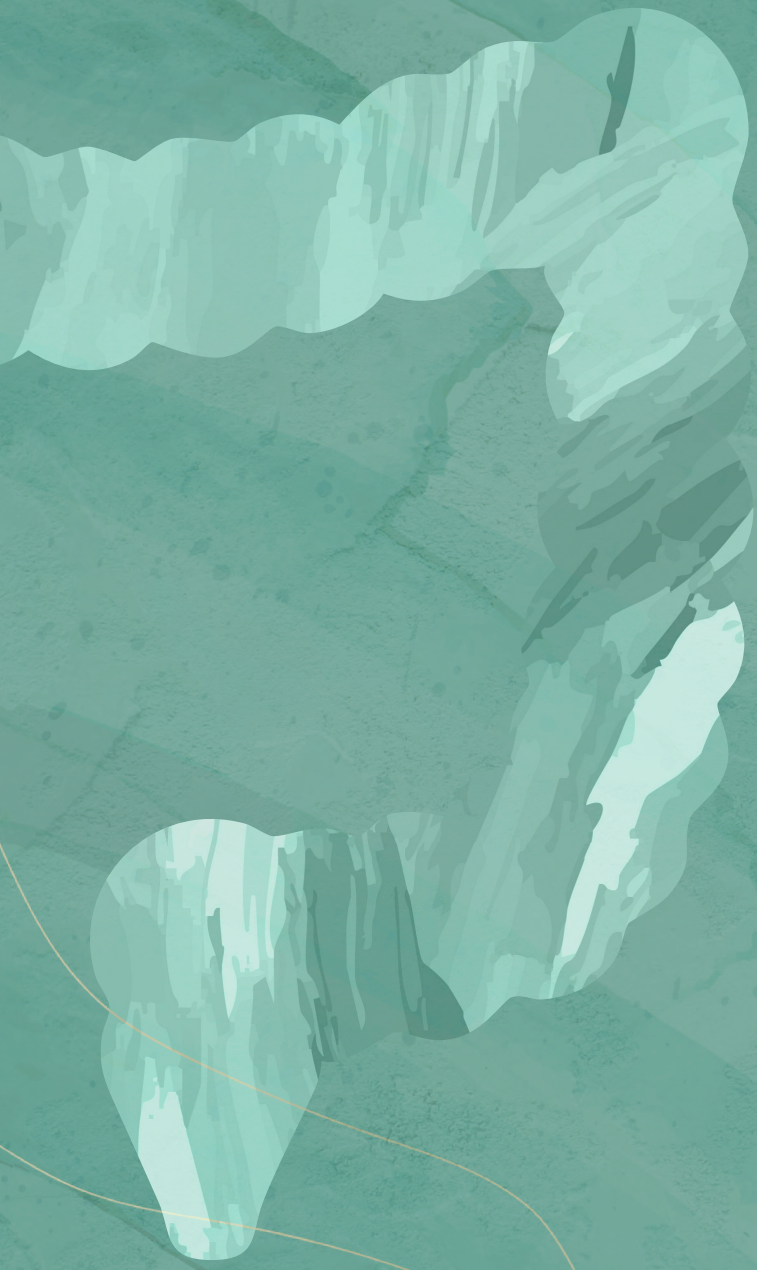
PhD portfolio

Department: Gastroenterology and Hepatology
PhD period: 02/06/2020 – 04/09/2024
PhD Supervisor(s): Prof. J.P.H. Drenth, Prof. F. Hoentjen
PhD Co-supervisor(s): Dr. M. te Groen

Training activities	Year	Hours
Courses		
– Active Bystander Training for PhD candidates and postdocs	2023	1.5
– eBROK	2020	42
– Feedback training	2020	4
– Radboud in'to Languages – Arabic course 'op weg naar A1'	2023	28
– Radboud in'to Languages – Arabic course 'A1'	2023	28
– Radboudumc - Introduction day	2020	6
– Radboudumc - Scientific integrity	2023	20
– RIMLS – Introduction course - In the lead of my PhD	2021	15
– Voice and presentation training by Debby Mureau	2021	8
– Workshop 'excellente gespreksvoering' omtrent rekruteren van patiënten	2020	4
Seminars		
– GI-Hep meetings with research experts	2020-2023	10
– Radboud Research Rounds – Tumors of the digestive tract	2021	1.5
– Research Integrity Rounds	2021	1.5
– Research Integrity Rounds	2022	1.5
– RIMLS PhD retreat	2023	24
– RIMLS Meet the Expert	2021	1
– Soeterbeeck regional GI seminars	2020-2024	28
Conferences		
– Digestive Disease Week, San Diego (oral and poster presentation)	2022	48
– Digestive Disease Week, Washington D.C. (poster presentation)	2024	48
– ECCO congress, virtual (poster presentation)	2022	40
– ECCO congress, Copenhagen (poster presentation)	2023	40
– NVGE Digestive Disease Days, virtual	2021	16
– NVGE Digestive Disease Days, virtual (oral presentation)	2021	24
– NVGE Digestive Disease Days, Veldhoven (poster presentation)	2023	24
– Young-ICC, post ECCO symposium	2022	3
Other		
– Gastroenterology Research Meeting	2020-2024	252
– IBD Research Meeting	2020-2024	252
– Journal Club	2020-2024	252
Total		**1223**

BROK: Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers, ECCO: European Crohn's and Colitis Organisation, GI: gastrointestinal, GI-Hep: gastrointestinal and hepatology, IBD: inflammatory bowel disease, ICC: Initiative on Crohn and Colitis, NVGE: Nederlandse Vereniging voor Gastroenterologie, RIMLS: Radboud Institute for Molecular Life Sciences,



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