Thesis

European Network of Gastrointestinal Pathology Survey on Inflammatory Bowel Disease

submitted by

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Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, 14th of February 2023 Andrea-Noémi Wergner eh.

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Abstract in german

Einleitung

Die histopathologische Untersuchung gastrointestinaler Proben stellt einen wichtigen Schritt in der Diagnostik chronisch-entzündlicher Darmerkrankungen dar. Die vorliegende Studie evaluiert die diagnostische Herangehensweise und die pathologische Befundung der Proben im europäischen Vergleich.

Material und Methoden

Das European Network of Gastrointestinal Pathology (ENGIP) führte im Jahr 2016 eine online- Umfrage mit 60 Multiple-Choice Fragen zum Thema chronisch-entzündlicher Darmerkrankungen unter den Mitgliederinnen und Mitgliedern durch. Die Umfrage erfasste, wie Biopsiematerial eingesandt wird, und inkludierte Fragen zu histologischen Kriterien, diagnostischer Praxis und makroskopischer Aufarbeitung von Operationspräparaten.

Ergebnisse

185 Fragebögen aus 36 verschiedenen Ländern wurden ausgewertet. In 91.2% werden Biopsien aus verschiedenen Lokalisationen in separaten Behältern eingesandt, in 30.4% aus fünf oder mehr Lokalisationen. In 10.3% der Fälle wird lediglich eine Biopsie pro Darmsegment eingesandt, in den übrigen Fällen bis zu fünf. Endoskopische Befunde werden in 35.0% der Fälle der Pathologie übermittelt, die Dauer der Symptome in 37.7%. Über die bisherige Therapie wird die Pathologie in 25.3% informiert. Bei Colitis ulcerosa geben 94.0% der teilnehmenden Pathologinnen und Pathologen einen Aktivitätsgrad an, bei Morbus Crohn 78.0%. 63.7% wenden dabei kein in den Leitlinien empfohlenes validiertes Graduierungssystem an. 98.9% graduieren den Dysplasiegrad neoplastischer Läsionen.

Diskussion

Die Zahl der Biopsate unterscheidet sich im internationalen Vergleich, oft werden den Pathologinnen und Pathologen die in den Leitlinien empfohlenen klinischen Informationen nicht geliefert. Die Bestimmung der Krankheitsaktivität erfolgt mehrheitlich, doch finden dabei die in den Leitlinien empfohlenen publizierten validierten Graduierungssysteme wenig Verwendung. Ein Dysplasie-Grading wird konsequent durchgeführt.

Abstract in english

Introduction

The histopathologic examination of biopsies obtained from the gastrointestinal tract plays an important role in the diagnosis of inflammatory bowel diseases. This study aimed to evaluate the current approach to biopsy diagnosis among pathologists across Europe.

Materials and Methods

The European Network of Gastrointestinal Pathology (ENGIP) performed an online survey among its members in the year 2016. The survey consisted of 60 multiple-choice questions regarding inflammatory bowel disease. It evaluated how the biopsy material is referred to pathology and included questions on morphological criteria, standard histological diagnosis and reporting as well as the macroscopic workup of resection specimens.

Results

185 replies were received from 36 different countries. Biopsies from different sites are in 91.2% submitted in separate containers. In 30.4% of the cases, five or more sites are targeted. One biopsy per site is sampled in 10.3%, in the remaining cases up to five biopsies are received per site. Endoscopic findings are provided in 35% of the cases, duration of symptoms in 37.7%. The treatment history is known in 25.3%. Grading of disease activity is performed 94% of cases with ulcerative colitis and in 78.0% of cases with Crohn’s disease. Of note, 63.7% of pathologists do not apply a validated grading scheme, as recommended in international guidelines. Dysplasia is graded in 98.9%, preferably applying a two-tiered system.

Discussion

The number of biopsies and the biopsy handling vary among countries. Often, pathologists do not receive the clinical information that is regarded necessary for appropriate work-up according to international guidelines. The disease activity is graded commonly, but widely without use of published validated scoring systems that are recommended in international guidelines. Grading of dysplasia is almost always performed.

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List of abbreviations

5-ASA	5-Aminosalicylic-Aacid
APCs	Antigen Presenting Cells
APC	Adenomatous polyposis coli gene
CARDs	Caspase Recruitment Domains
CCR6	Chemokine receptor 6
CD	Crohn's Disease
CD1d	Cluster of Differentiation 1d
CRC	Colorectal Carcinoma
CRP	C-reactive Protein
ECCO	European Crohn's and Colitis Organization
ENGIP	European Network of Gastrointestinal Pathology
ESP	European Society of Pathology
ESPGHAN	European Society for Pediatric Gastroenterology, Hepatology and Nutrition
FEG	Focal Enhanced Gastritis
GIT	Gastrointestinal Tract
H&E	Hematoxylin-Eosin
IBD	Inflammatory Bowel Disease
IFN- γ	Interferone gamma
IL-5	Interleukin 5
IL-13	Interleukin 13
IL-17	Interleukin 17
IL-23	Interleukin 23
JAK2	Janus Kinase 2
K-ras	Kirsten rat sarcoma virus gene
LRRs	Leucine-rich Repeats
LPS	Lipopolysaccharide
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NOD2	Nucleotide-binding oligomerization domain-containing protein 2
NSAIDs	Non-steroidal anti-inflammatory drugs

PAS	Periodic acid–Schiff
TGFβ	Transforming growth factor beta
TH2-Cells	TH-2 Helper Cells
TH1-Cells	TH-1 Helper Cells
TH17-Cells	TH-17 Helper Cells
TNF	Tumor Necrosis Factor
UC	Ulcerative Colitis
STAT3	Signal transducer and activator of transcription 3
p53	Tumor protein p 53
hMLH1	human mutL homolog 1
p16INK4a	cyclin-dependent kinase inhibitor 2A
p14ARF	p14 alternate reading frame
SCENIC	Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International consensus recommendations
TGFβRII	transforming growth factor beta receptor II

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1. Introduction

Ulcerative Colitis (UC) and Crohn's Disease (CD) both represent the two main types of inflammatory bowel disease (IBD) with characteristic pathological and clinical features (1), (2). UC is characterized by diffuse mucosa-restricted chronic inflammation. It usually affects the rectum and extends continuously towards proximal parts of the colon. CD shows transmural and discontinuous inflammation with potential involvement of any part of the gastrointestinal tract (2), (3).

1.1 Inflammatory Bowel Disease

1.1.1 Epidemiology

Incidence and prevalence of IBD tend to be the highest in Northern Europe, North America, the United Kingdom, and Australia (4). Approximately 0.3% Europeans (2.5-3 million people) are affected by IBD (5). According to Gajendran et al. IBD is currently affecting around 1.5 million people in the United States (6). Lophaven et al. reported an increase of the incidence of CD from 5.2/100,000 to 9.1 and of UC from 10.7 to 18.6/100,000 in Denmark from 1980-2013 (7). Gihone and co-workers conducted a population-based study which showed rising incidence of IBD of French adolescent and pediatric patients (between 10-16years) between 1988 and 2011 (8). A systematic review of Siew Ng et. al. demonstrated that Norway had the highest prevalence values for UC (505 per 100,000) and Germany the highest for CD (322 per 100,000). Newly industrialized and progressively westernized countries in Asia, Africa, and South America also registered a rising incidence of IBD (9). IBD has a significant impact on the patient's social and economic aspects of life since 20% in Europe have to face employment problems and long-term disability. Furthermore IBD causes substantial economic and healthcare costs (5), (10). Although IBD also occurs in elderly patients, peak age for UC has been shown to be 30-40 and for CD 20-30 years (11). Familiar clustering has been reported for IBD ranging from 2% up to 16% (12). Up to 22.5% of IBD patients have a family member with a history of IBD. In this case affected individuals often develop the disease much earlier (13). Furthermore, prevalence of IBD tends to be higher in Jewish population compared to other ethnicities (6), (13), (14).

1.1.2 Etiology and Pathogenesis

The pathophysiology of IBD is very complex and is still not entirely understood. However, genetic susceptibility, environmental factors and alterations of the gut microbiome play an important role in disease pathogenesis leading to the host's chronic immunologic dysregulation (15) (16). IBD is characterized by an irregular T-cell mediated chronic immune response with different predominant cell types and cytokine profiles in UC and CD. In CD, TH1 and TH17 T-cells play the predominant role in the inflammatory process. Antigen-presenting cells (APCs) produce TGFβ, IL-18 and IFN-γ which induces IL-12 secretion promoting subsequent T-cell differentiation. In UC, mostly TH2-cells have been found to induce mucosal inflammation, also through secretion of IL-5 which enhances the activation of B-cells (15), (17). CD1d-associated natural killer cells producing IL-13 have been found to induce a activation of atypical TH2-cell immune response in UC (18).

1.1.2.1 Genetic Factors

163 IBD related genetic loci have been discovered in a genome wide analysis out of which 110 are linked to both UC and CD, 30 to CD and 23 to UC, respectively (19). The gene loci linked to IBD pathogenesis encode proteins for mucosal barrier function, immune response and regulation, autophagy and metabolic and signaling pathways. The nucleotide binding oligomerization domain 2 gene (NOD2) on chromosome 16 is expressed primarily in monocytes and activates Nuclear Factor kB (NF-kB) by its N-terminal caspase and recruitment domains (CARDs) and carboxy-terminal leucine-rich repeat domains (LRRs) (20). Bacterial lipopolysaccharides induce NF-kB-activation in cells by interaction with NOD2 (21). Frameshift mutations of NOD2 have been demonstrated to bear a higher risk for individuals to develop CD by causing inappropriately increased immune response to bacterial LPS (22). Single nucleotide polymorphisms (SNPs) in the genes of JAK2 or STAT3 and IL12B, TNFSF15, and CCR6 are part of the downstream signaling pathway of IL23 predispose to the development of CD and partly also of UC (23), (24).

1.1.2.2 Gut Microbiome

Altered composition of the intestinal microbiome due to an increased bacterial population in total with a decreased biodiversity has been proved to have a substantial impact on disease pathogenesis of IBD (18), (25), (26). Microbial dysbiosis alters the mucosal permeability and shifts the microbial population towards species with increased inflammatory capacity. This leads to enhanced bacterial invasion, subsequent tissue damage and a chronic inflammatory response through abnormal interaction between host cells and intestinal microbes (15), (25), (27).

1.1.2.3 Environmental Factors

Cigarette smoking seems to have a protective effect against UC with a 50% lower risk for hospitalization, but on the other hand, smokers have a higher risk for developing CD (28), (29). Certain medications have been proven to influence the risk for IBD: Oral contraceptives are associated with a higher risk for both UC and CD (30). Studies have shown that consumption of antibiotics in childhood increases the risk of developing CD later on by altering the diversity of intestinal gut flora (31), (32), (33). The use of Non-steroidal anti-inflammatory drugs (NSAIDs) harbor a higher risk for developing IBD, higher relapse rate and an increased risk for emergency admission of IBD patients (34), (35), (36). Dietary habits are also known as pathogenetic environmental factors: Increased sugar intake is associated with higher incidence of CD (37). Total polyunsaturated fatty acids, omega-6 fatty acids, and meat rise the probability to develop IBD by altering the microbiome and antigen presentation (38).

1.1.3 Clinical Manifestation

1.1.3.1 Disease Phenotype

UC affects the rectum and extends proximally towards the colon in a continuous fashion with decreasing severity (39). Disease extent can be variable: At the time of diagnosis, in 30%-50%, UC is restricted to the rectum, 20-30% of the patients have left-sided colitis and about 20-30% have pancolitis (40). The Montreal classification is based on the maximal macroscopic dissemination of UC and divides disease extent into three categories: Proctitis (E1), left-sided disease (E2) and extensive disease (E3). Disease severity is classified upon clinical symptoms into five levels (S0-S4) based on number of bloody stools, temperature, pulse and hemoglobin levels (41). Although disease extent may change over time, extensive disease is associated with a higher hospitalization rate and disease activity (42). Insufficiency of the ileocecal valve might be the cause of washed back colonic content into the ileum causing backwash ileitis (2).

Any part of the GIT can be affected by CD. Approximately 25% of the patients develop solely colonic involvement, 25% ileitis and about 50% present with ileocolitis (6). Up to 75% of CD patients develop perianal involvement in the course of disease. Perianal involvement is associated with more aggressive disease course, faster development of stricturing or penetrating complications and a higher risk for extra intestinal manifestations (43), (44), CD can be divided into primary stricturing or penetrating phenotype or inflammatory, depending on the predominant complications (45), (46), (47). Disease can progress over time into stricturing or penetrating disease or into a mixed type. Thia et al. demonstrated a rising cumulative incidence of either complications over time of 18.6% after 90 days, 22.0% after one year, 33.7% after five years and 50.8% after 20 years after the first diagnosis (45). Schwartz et. al demonstrated a cumulative risk for fistulae of 33% after 10 years and of 50% after 20 years (46). Manifestations of fistulae can be enteroenteric, enterocutaneous or enterovesicular (48). CD can affect the esophagus, the stomach or the duodenum as upper GIT manifestation either solely or combined with other localizations (49). gastric inflammation has been identified microscopically in up to 70% of CD patients (50) (51). Children usually suffer from greater disease extent and more frequent upper gastrointestinal tract involvement.

Earlier disease onset in children and adolescent patients is often associated with an increased disease severity (52). The phenotype of CD is classified according to the Montreal classification which comprises age of onset (A1-3), disease location (L1-4) and behavior (B1-3) (41).

1.1.3.2 Symptoms

UC typically presents with abdominal pain, diarrhea and bloody stools, occasionally with mucus. Lethargy, weight loss, anorexia and night sweats may also occur (53), (54), (55). Severity of clinical symptoms is higher in anatomically more extended disease and harbors a higher cumulative risk for complications and the necessity for surgical therapy (56). Patients with UC suffer in 10% of from severe bleeding, in 1-3% from massive hemorrhage (48). Toxic megacolon, a colonic dilatation on radiologic imaging, occurs in approximately 15% of UC patients requiring urgent surgical therapy due to the risk of bleeding, perforation, and sepsis (48), (57).

Patients with CD commonly present with symptoms of abdominal pain, weight loss, malabsorption, and watery or bloody diarrhea, in case of disease manifestation in the rectum or colon. The abdominal pain tends to relieve after bowel movement and is often colic-like or can even mimic appendicitis (48). Fever is also common in CD patients; often indicating an ongoing inflammatory process, an infection in the bowel, or in severe cases, perforation or an intraabdominal abscess (6). Fibrostenotic manifestation of CD leads to the development of strictures causing obstructive symptoms, nausea and vomiting (48). Perianal lesions with ulcers, fissures, fistulae, or abscesses and strictures in the anal canal arise in up to 75% in the course of disease (58). Perianal fistulae have been reported in 20-25% of CD patients with ileal disease and in 60% of CD patients with rectal involvement (59).

Extraintestinal manifestations in IBD have been demonstrated to occur in a range from 6 up to 47% (60), (61), (62), (63). They may present as peripheral arthritis, axial arthropathies or dermatologic manifestations (erythema nodosum, pyoderma gangrenosum, aphthous stomatitis or Psoriasis). Furthermore, iritis, uveitis, anemia or primary sclerosing cholangitis are also common (64), (65).

1.1.4 IBD-associated Colorectal Carcinoma

One of the most serious complications of UC is the development of colorectal carcinoma (CRC) (66), (67), (68). IBD-associated CRC causes approximately 15% of all deaths in this patient group and constitutes 1-2 % of all CRC in general population (69), (70). A large meta-analysis from Eaden et. al. demonstrated an overall prevalence rate for the development of CRC in UC patients of 3.7% with a cumulative incidence of 2% by 10 years, 8% by 20 years and 18% by 30 years (71). Young age at colitis onset, extensive colonic involvement, long disease duration and concomitant primary sclerosing cholangitis have been demonstrated as risk factors for UC-associated CRC (72), (73). Carcinomas arising in UC tend to affect younger individuals, are more often poorly differentiated, and occur predominantly in the right colon (74).

CD harbors also a higher risk of developing small bowel cancer (75), (76). The incidence of CRC in CD patients is estimated to be six times higher than in general population. Cancer arising in perianal strictures of CD patients has been reported, which had been adenocarcinoma in 59% and squamous cell carcinoma in 31% (59).

IBD-associated CRC often shows synchronous multifocal dysplasia in areas remote from the tumor (77). CRC arising in IBD differs in genetic alterations and molecular characteristics from sporadic CRC in patients without IBD (78). Acquisition of early p53 mutations, hyper-methylation of hMLH1, p16INK4a, and p14ARF in IBD associated CRC are characteristic steps in genetic carcinogenesis as well as frequent TGFβRII mutation through microsatellite instability caused by chronic inflammation (72), (79), (80). APC and K-Ras mutations are less frequently observed in carcinogenesis of IBD-associated CRC in contrast to sporadic CRC (81).

1.1.5 Therapy

1.1.5.1 Drugs for IBD treatment

Medical treatment should be adapted on disease severity and extent and is divided into induction therapy and remission therapy (6). 5-ASA tablets combined with enemas are recommended for mild to moderate UC and have been proven to be more effective than monotherapy. Tumor Necrosis Factor (TNF) inhibitors (Infliximab, Adalimumab, Certolizumab pegol and Golimumab) are effective in induction and maintenance therapy and are recommended as first line therapy for severe CD with perianal involvement. (82), (83). Glucocorticoids (prednisolone or hydrocortisone) are potent immunosuppressants which are effective in induction of remission and fast symptom relief. (6). They are indicated after failure of oral 5-ASA therapy and for moderate to severe disease activity in UC (84). Azathioprine or 6-mercaptopurine and methotrexate are suitable for maintenance of remission in UC and CD (82).

1.1.5.2 Surgery in IBD treatment

UC patients require in 30-40% surgical therapy and patients with CD will need in up to 80% surgical treatment in their course of disease (85). Surgical intervention is more likely necessary in ileal and ileocolonic CD with perianal affection (86) and is required in case of abscesses, complex fistulae, fibro-stenotic strictures causing bowel obstruction or insufficient medical therapy (87). Patients with dysplastic lesions that are endoscopically unresectable, or have multifocal or high grade dysplasia or CRC, should undergo proctocolectomy (88), (89).

1.2 Elements of Clinical Diagnosis in IBD

1.2.1 Endoscopy

Endoscopy with obtaining biopsies is the current gold standard for initial diagnosis of IBD. Chromoendoscopy with methylene blue dye improves detection of lesions suspicious for dysplasia (87). Furthermore, endoscopy plays an important role in surveillance of dysplasia and IBD-associated CRC, monitoring treatment effects and disease activity. Edema, erythema, mucosal granularity and friability, erosions, ulcers, and pseudopolyps may be present in UC upon colonoscopy. Although CD may show similar findings, aphthous ulcers, cobblestoning, and discontinuous or skip lesions are very characteristic findings in CD (90).

1.2.2 Laboratory findings and stool tests

Serology tests may show anemia and vitamin B12, - or iron deficiency. Elevated C-reactive protein (CRP) is a surrogate marker for active disease and is a good predictor for disease relapse and remission in CD (91). Calprotectin is a good marker for assessment of disease activity in IBD patients and is correlated with an increased risk of disease relapse and endoscopic disease activity (92), (93), (94). In case of diarrhea, stool examinations and bacterial cultures should be ordered to check for pathogenic bacteria, fungi, parasites or viruses considering the differential diagnosis of infectious colitis (82).

1.2.3 Radiologic imaging

Computed tomography and Magnetic resonance imaging with contrast material are standard radiologic procedures with high diagnostic accuracy to examine the small bowel in CD. Radiologic imaging is especially helpful in negative ileal endoscopy to detect strictures, abscesses, obstructions, inflammatory changes and ulcers in the small bowel (48), (95), (96).

1.3 Pathology in IBD diagnosis

1.3.1 Macroscopic features of UC

The colonic mucosa in untreated UC typically shows an inflamed granular and edematous surface, as well as hyperemia, and ulcerations. In further course of disease, the mucosa becomes atrophic with a loss of haustration. Fulminant colitis may show an inflamed serosa. A distinction between UC and CD can be challenging in fulminant colitis. The inflammatory damage in UC tends to be more severe in distal parts of the colon (39), (97), (98). UC affects the mucosa in a diffuse and continuous fashion, sharply delimited from the unaffected normal areas, usually without skip lesions. Normal mucosa in between recessed spacious ulcerations give the impression of so called pseudopolyps. Rectal sparing, a cecal patch or backwash ileitis may also occur (39), (98), (99).

1.3.2 Macroscopic features of CD

CD frequently affects the terminal ileum along with the right colon and presents with ileocolonic, isolated colonic or ileal disease in approximately one third of the patients, respectively (98), (100). CD is macroscopically characterized by the development of transmural segmental lesions with a discontinuous and focal distribution. Skip lesions are seen in-between unaffected mucosal areas or bowel segments (98). Early macroscopically visible findings are small aphthous ulcers which extend into large serpiginous, linear, or bear-claw shaped ulcers or large deeply fissuring ulcers. The surrounding edematous mucosa creates the macroscopic appearance of “cobblestones”. Healing ulcers leave depressed longitudinal “rail-track” scars (39), (58), (98). Segmentally thickened, rigid, stricktured bowel wall is frequent as a consequence of fibrosis and fibromuscular proliferation or edema. Fissures, fistulae, adhesions to other colonic segments, or bowel organs are characteristic macroscopic findings of CD (39), (58), (98). The affected serosal surface often shows a hyperemic, opaque appearance or overlying inflammatory exudate (39), (58), (99). Occurrence of adipose tissue in the antimesenteric areas of the bowel wall, also referred to as “fat wrapping”, has been demonstrated to be a pathognomonic feature of CD (99) (101), (102).

1.3.3 Microscopic features of UC

Microscopically untreated UC is characterized by a diffuse and continuous disease involvement. The lamina propria shows an evenly distributed mucosa-restricted inflammatory infiltrate, which is rarely expanding to the upper submucosa. Predominant cells of the inflammatory infiltrate are lymphocytes and plasmacells, and a variable number of eosinophils and neutrophilic granulocytes. The amount of neutrophils depends on the degree of disease activity (99), (103). Additional features of chronicity in IBD include basal plasmacytosis, pathologic alterations of crypt architecture and metaplastic changes (103), (104). Basal plasmacytosis is defined by accumulation of plasma cells between the lamina muscularis propria and basis of the crypts (99), (105). This finding has the strongest predictive value for IBD and turned out to be one of the earliest microscopic signs of UC. Schumacher et al. showed in their study that in 38% of the UC patients basal plasmacytosis in rectal biopsies occurred two weeks after symptom onset (106). Eosinophilic granulocytes may be present a variable number (1), (107). Villanacci et al. demonstrated the presence of at least one-three eosinophils in-between the basally located plasma cells in cases with basal plasmacytosis in IBD specimens. However, their exact role in the inflammatory process is not clarified yet (108). UC leads to distortion of crypt architecture which may be present as loss of their parallel alignment, variability in crypt diameter or crypt dilatation. The crypts are disorganized and lose their characteristic “test tube appearance”. Crypts also become atrophic (shortened) with wider distance between lamina muscularis mucosa and their basis (107) (109). Crypt branching is a regenerative process in which new crypts are formed by fission (110). It is present if two or more bifurcated crypts are observed in a properly oriented section containing at least 2mm of lamina muscularis mucosae (99), (111). Metaplastic changes like pyloric gland metaplasia at any site or Paneth cell metaplasia in the left colon reflect chronic inflammatory tissue damage in UC (104).

Colonic mucosa displays signs of chronic and/or active colitis depending on disease phase. In active disease neutrophilic granulocytes invade the lamina propria and cause tissue damage to the crypts and surface epithelium. Crypt injury is represented by cryptitis (neutrophils invading crypt epithelium) or crypt abscesses (neutrophils and necrotic debris in the crypt lumen). Ruptured crypts may give rise to the development of a granulomatous tissue reaction which should not rise suspicion for CD. Severe inflammatory damage can cause surface erosions or ulcerations. Figure 1 shows the characteristic microscopic appearance of active UC. Lamina propria hemorrhage or edema as well as regenerative epithelial changes (mucin depletion) are also signs of active disease (103). Compared to CD, UC displays more severe architectural abnormalities and more frequent crypt abscesses (1). In quiescent disease architectural abnormalities (crypt atrophy and shortening, decreased crypt density) or metaplastic changes usually persist and active inflammation with neutrophilic infiltration of the lamina propria with crypt damage (cryptitis, crypt abscess) is absent. Basal plasmacytosis tends to regress (1), (99), (104). Christensen et. al. defined histologic quiescence as features of chronicity being present without active inflammation and histologic normalization as normally looking colonic mucosa. Her study group demonstrated a higher relapse-free survival of UC patients in histologic normalization than in quiescent disease (112). Histologically, backwash ileitis has been described as mild patchy neutrophilic inflammation of the ileal lamina propria with crypt abscesses, cryptitis, regenerative changes and villous atrophy (2), (113). The adjacent caecum in cases of backwash ileitis has been showed to have a similar or more severe degree of activity (114). Rectal sparing or normalization of rectal mucosa, patchiness and discontinuity are well-known treatment related effects in UC. In this case, caution is warranted not erroneously change the diagnosis from UC into CD (1), (104).

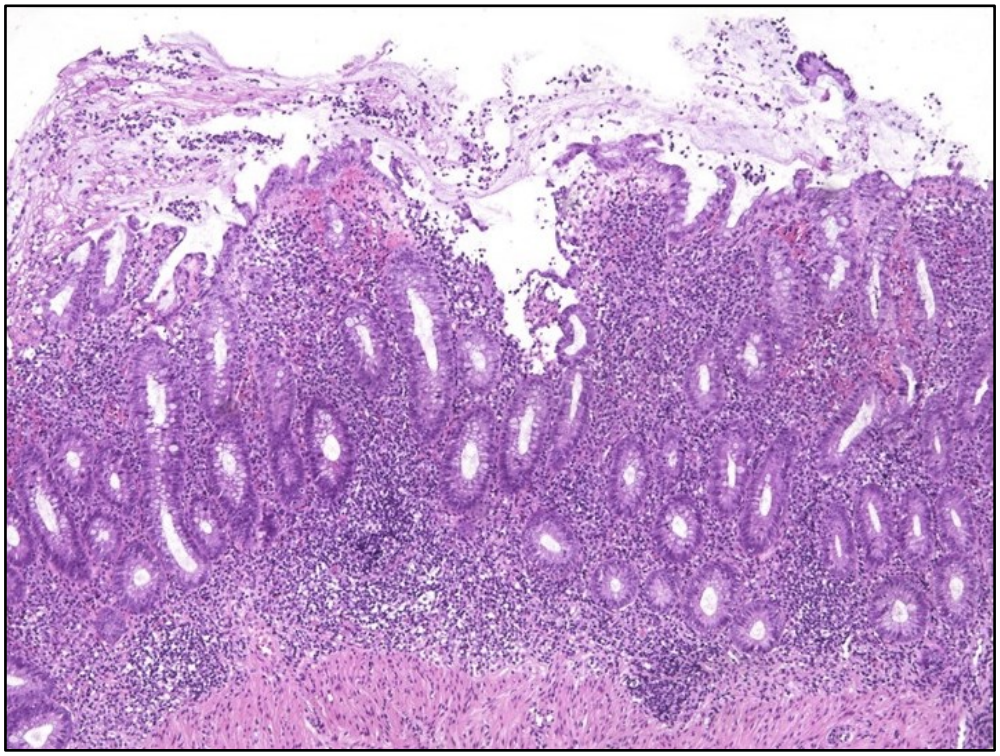


Figure 1: Active ulcerative colitis with architectural distortion, diffuse inflammatory lymphoplasmacytic infiltrate with basal plasmacytosis, cryptitis, crypt-damage and erosions (Courtesy of Dr. Langner).

1.3.4 Microscopic features of CD

CD displays a discontinuous (separated by anatomically normal areas) transmural and focal inflammatory infiltrate by plasmacells and lymphocytes with focal crypt architectural irregularities (crypt distortion and crypt branching) (99), (115). Basal plasmacytosis, the presence of plasma cells between the crypt bases and the muscularis mucosae and is an early and highly predictive sign of IBD (106). Infiltration of the lamina propria by neutrophils, cryptitis, crypt abscesses or injury of the surface epithelium are signs of disease activity (99). Deep fissures and ulcers are common, caused by transmural inflammatory damage (1). Aphthoid ulcers are early and characteristic findings of active CD (116). Granulomas are defined as clustered formations of histiocytes with or without necrosis or giant cells. They are considered as a diagnostic hallmark of CD when not associated to crypt injury or foreign material (98), (117). The presence of granulomas is proven to be highly specific for CD and is more frequent in pediatric CD patients at colonoscopy than in adults (53.8% vs 17.6%) (118). Transmural lymphoid aggregates can be observed in resection specimens (1), (116). The bowel wall may be thickened due to edema, fibrosis and muscular and neuronal hypertrophy (119). Focal and discontinuous crypt distortion and atrophy are a characteristic for CD but less severe than in UC (1), (107), (120). Figure 2 shows the characteristic histologic features of active CD.

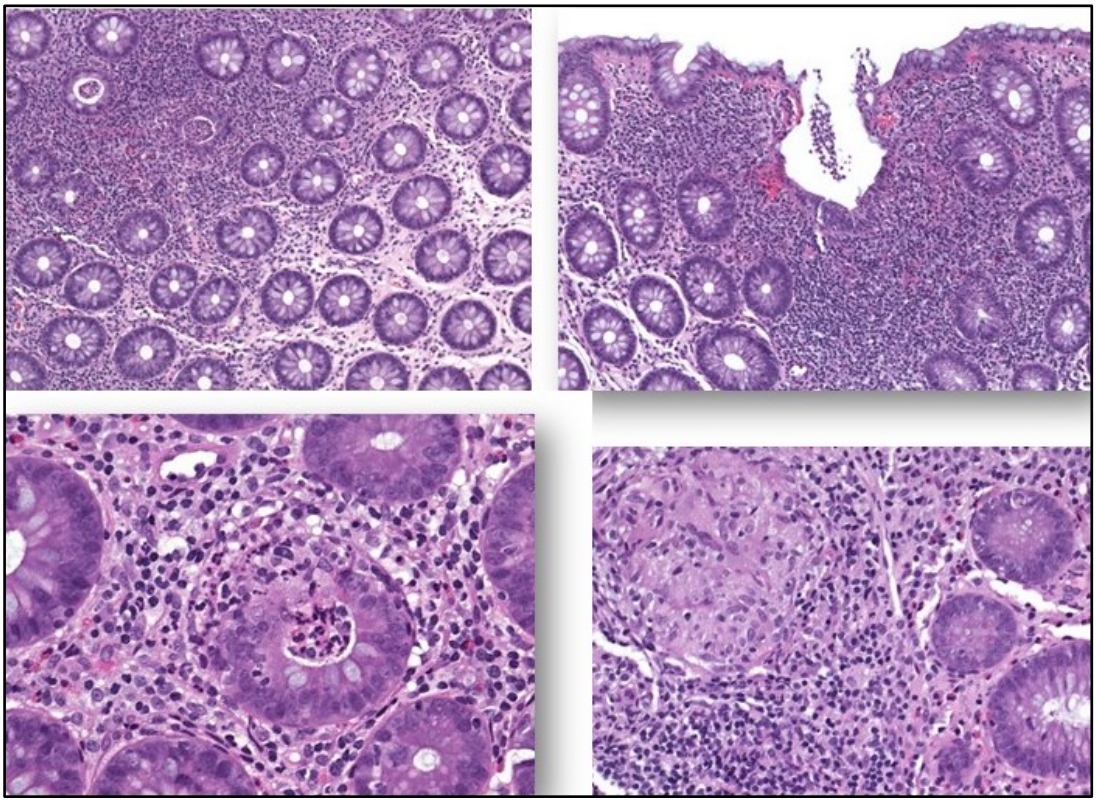


Figure 2: Crohn's disease: Upper left: Focal (discontinuous) colitis; Upper right: Aphthoid erosion; Lower left: Crypt abscess; Lower right: Epitheloid granuloma. (Courtesy of Dr. Langner)

1.3.5 Microscopic features of dysplasia in IBD

Colitis associated dysplasia develops due to chronic inflammatory damage with differences in carcinogenesis and often multifocal development compared to sporadic dysplasia (78). Pathogenesis of IBD-associated CRC is based on a chronic inflammation-dysplasia-cancer sequence (121). Dysplasia is defined by Riddell. et. al. as an “unequivocal neoplastic alteration of the colonic epithelium” and diagnostically categorized into four groups: negative for dysplasia, indefinite for dysplasia and positive for low,- or high-grade dysplasia. The histological characteristics for dysplasia are related to dysplastic lesions of tubular adenomas in non-IBD specimens (122). Low-grade dysplasia characteristically shows enlarged, hyperchromatic nuclei with increased nuclear-to-cytoplasmic ratio and an increased mitotic rate. High-grade dysplasia displays more severe cytologic and architectural abnormalities with crowded, pleomorphic and hyperchromatic nuclei without polarization, and glands with “back-to-back” or cribriform growth (77). Dysplasia is named as indefinite if no clear distinction can be made between low-grade dysplasia and regenerative epithelium due to overlapping features, in cases of densely inflamed areas or inadequate sample orientation. Adenomatous, villous or serrated forms of dysplasia can be distinguished in IBD-associated dysplasia (123).

1.3.6 Diagnostic significance of pathologic examination

Histopathologic examination of IBD specimens plays an important role in establishment of IBD diagnosis, and differentiation between UC and CD. Furthermore, identifying and grading of dysplastic lesions and assessment of entire disease distribution is based on histologic confirmation. The pathologists contribution to diagnosis impacts the patient's treatment regimen (39), (82), (124), (125). Detection of dysplastic lesions or CRC determines the patient's subsequent surveillance interval and therapeutic management (proctocolectomy vs. polypectomy) (88), (126), (127). Achievement of mucosal healing upon endoscopy and clinical remission are most important treatment goals to improve quality of life and avoid complications, disease relapse and requirement for surgery (6), (40). Mucosal healing at a histological level, however, does not equal endoscopic healing, but it is still not regarded consistently as treatment goal yet and lacks a widely standardized definition. There is growing evidence that histological healing is a better predictor for complication rates and disease relapse with high sensitivity (128), (129), (130), (131). Furthermore, assessment of disease activity upon histology may be useful in predicting disease course and evaluating therapeutic success (132). The European Crohn´s and Colitis Organization (ECCO) and the European Society of Pathology (ESP) have published consensus guidelines with recommendations on histologic diagnosis and reporting of IBD upon biopsies and surgical specimens (109), (126), (133), (134), (135).

1.4 Aim of the study

To date, there is little information about current diagnostic practice and guideline adherence in daily routine among pathologists in Europe. Therefore, the European Network of Gastrointestinal Pathology (ENGIP) designed an online survey on Inflammatory Bowel Disease. ENGIP was founded in 2012 by members of the Working Group of Digestive Diseases of the European Society of Pathology (ESP). It serves as a platform for pathologists to share information about upcoming courses, guidelines, and consensus papers in the field of gastrointestinal pathology. Moreover, the organization enables international networking among pathologists. In November 2020 ENGIP counted 570 members from 48 different countries (https://www.medunigraz.at/engip[accessed 10.01.2023]).

The study aimed to evaluate current diagnostic practice and reporting of IBD specimens as well as theoretical opinions in IBD pathology of ENGIP members across Europe. Furthermore, the questionnaire assessed how the clinicians sent their biopsy material to the pathologic institutions. The study attempted to portray the fields of consent and disagreement regarding histological features, definitions of terms for reporting histological findings as well as general aspects about IBD pathology among its participants. Furthermore, the study intended to assess the pathologist`s overall guideline adherence for routine IBD diagnosis and at which extent guideline recommendations for biopsy handling are followed by the clinicians. Based on these data the survey may contribute to the development and refinement of further guidelines.

2 Materials and Methods

Members of the steering committee and advisory board of ENGIP have proposed a web-based survey for pathologists about Inflammatory Bowel Disease. ENGIP members received an invitation email with a link to the online survey which was accessible between May and July 2016. The survey evaluated the participant's theoretical knowledge and practical approaches in microscopic diagnosis and reporting of suspected or confirmed IBD. Furthermore, the questionnaire covered macroscopic handling of resection specimens from IBD-patients. It also assessed the conditions under which pathologists receive their biopsy material, referring to the clinician's biopsy handling and provided patient related information. The ENGIP survey has been an online anonymous questionnaire composed of 60 questions (Q). The answers were designed in a multiple-choice (MC) fashion. Depending on the type of question, either one or multiple answers could be chosen. Participants were free to skip questions. These were not included into the interpretation of the data. Categorial variables of the 60 results were represented in absolute and relative frequencies. Approval from the local Ethics committee was not required for the present study.

The ENGIP survey covered six main topics:

1 Personal information (Q1-Q5)

2 Received biopsy material (Q6-Q13, Q19)

3 Provided clinical information (Q14-Q18)

4 Laboratory handling of tissue samples (Q20-Q22)

5 Theoretical knowledge and practical approach to histologic diagnosis of IBD (Q23-Q55)

6 Macroscopic work-up of IBD resection specimens (Q56-Q60)

The initial 1-5 questions of the survey covered personal information including country and institution of practice, educational level, and memberships in pathological associations as well as the kind of tissue material the pathologists generally deal with.

Questions 6-13 and 19 addressed how the participants usually received biopsy material from the clinicians in cases of suspected IBD. Specifically, the quantity of biopsies per site, the manner of collection in separate tissue containers and how frequent the terminal ileum and upper gastrointestinal tract are routinely sampled in the initial diagnostic workup of IBD patients.

Questions 14-18 referred to what kind of patient related information the clinicians usually provided the pathologists along with the biopsy material in cases with suspected IBD. These were patient's age, endoscopic findings, duration of symptoms, treatment history and the patient's immune status.

Questions 20-22 covered laboratory handling of IBD specimens in terms of orientation, sectioning, and standard staining of IBD specimens.

Questions 23-55 evaluated the participant's approach in histologic diagnosis and reporting of IBD specimens including theoretical interpretations and definitions of microscopic features of IBD. These included architectural abnormalities of crypts and surface epithelium, terms of describing inflammatory infiltrate. The questions also covered the diagnostic value of terminal ileitis, focally enhanced gastritis, rectal sparing, granulomas, and hallmarks of chronic and active colitis. Furthermore, the pathologist's individual approaches of diagnosing and reporting activity and dysplasia has been addressed.

The final questions 56-60 covered routine practice in macroscopic workup of resection specimen from IBD patients. Specifically, photographic documentation and sampling methods.

All questions from the survey are chronologically listed in Table 1.

Table 1: Questionnaire - ENGIP Survey on Inflammatory Bowel Disease

1. In which country do you practice?
2. Type of practice?
3. Your status?
4. Membership in societies and/or networking platforms?
5. Which types of IBD specimens do you deal with?
6. In a case of colonoscopy material, how do you usually get the biopsy specimens from different locations in a patient with suspected IBD?
7. In a case of colonoscopy material, how many containers (vials) do you usually get from a patient with suspected IBD?
8. What is the average number of biopsies per biopsy site?
9. Is the location of origin clearly indicated?
10. Do you get the biopsies from the rectum in a separate container?
11. Do you get the biopsy from the terminal ileum from a patient with suspected IBD?
12. Do you usually get biopsy material from the upper gastrointestinal tract from a pediatric / adolescent patient with suspected IBD?
13. Do you usually get biopsy material from the upper gastrointestinal tract from an adult patient with suspected IBD?
14. Do you receive clinical information regarding duration of symptoms?
15. Do you receive clinical information regarding patient's age?
16. Do you receive clinical information regarding endoscopic findings?
17. Do you receive clinical information regarding history of treatment?

18. Do you receive clinical information regarding the immune status of the patient?
19. Is the size of the samples you get adequate for analysis?
20. Do your technicians orient the biopsy specimens at embedding?
21. How many sections are usually cut?
22. Which staining(s) do you usually apply?
23. How do you assess mucosal architecture?
24. If you assess the surface, is the villiform change due to widening of the crypts?
25. Crypt distortion – how do you define it?
26. Crypt distortion – how many crypts must be involved?
27. Crypt atrophy – how do you define it?
28. How do you define colitis?
29. How do you define chronic colitis?
30. How do you assess the diagnostic value of granulomas in suspected Crohn's disease?
31. How do you assess the diagnostic value of terminal ileitis in suspected Crohn's disease?
32. How do you assess the diagnostic value of focally enhanced gastritis in suspected IBD?
33. Which elements of the cellular infiltrate are helpful for the diagnosis of IBD in the differential diagnosis to other forms of colitis?
34. "Basal distribution" of inflammatory cells means changes …
35. How do you define diffuse (continuous) inflammation?

36. How do you define discontinuous (focal) inflammation?
37. Do you make a distinction between focal and patchy inflammation?
38. The prevailing location of colonic Crohn's disease is the …
39. The prevailing location of ulcerative colitis is the …
40. Rectal sparing in suspected IBD …
41. Do you usually define disease activity in ulcerative colitis?
42. Do you usually define disease activity in Crohn's disease?
43. Which type of system are you using to disease activity?
44. Do you use a published scoring system to define disease activity (e.g. Geboes, Riley, Nancy)?
45. How do you rate the presence of neutrophils as feature for the assessment of disease activity?
46. How do you rate the location of neutrophils as feature for the assessment of disease activity?
47. How do you rate the presence of mucosal breaks (erosions, ulcerations) as feature for the assessment of disease activity?
48. How do you rate the presence of other epithelial abnormalities (regenerating, recovering epithelium) as feature for the assessment of disease activity?
49. In case of dysplasia, do you assess the grade (degree) of dysplasia?
50. Which type of system are you using to assess the grade (degree) of dysplasia?
51. Do you differ between colitis-associated and colitis-independent (sporadic) dysplasia?
52. Surface maturation is a feature of …

53. When presumed dysplastic changes are limited to the crypts (not present in the surface epithelium) …
54. Do you use p53 immunohistochemistry in the assessment of lesions suspicious for dysplasia?
55. Do you use MIB-1/Ki67 immunohistochemistry in the assessment of lesions suspicious for dysplasia?
56. In resection specimens with IBD, do you usually take a photo of the gross specimen?
57. In resection specimens with IBD, do you have strict recommendations or rules for tissue sampling in your department?
58. In resection specimens with IBD, how do you sample the inflamed mucosa?
59. In resection specimens with IBD, do you sample macroscopically normal mucosa (other than resections margins)?
60. In resection specimens with IBD-associated carcinoma, do you sample inflamed mucosa remote from the tumor to rule out / detect synchronous dysplasia?

3 Results

Personal information (Q1-Q5)

A total of 185 ENGIP members from 36 different countries had completed the online questionnaire, predominantly from European countries. Most replies were received from Italy (11.4%, n=21), Romania (11.4%, n=21) and Germany (8.7%, n=16), followed by Spain and the Netherlands (4.9%, n=9). Additionally, some replies came from countries outside of Europe like Australia, Canada, or the United States of America. Table 2 gives a detailed overview over the number of responding pathologists from different countries.

Table 2: Countries of practice

Countries of practice	Respondents in %	Number of Respondents
Australia	3,8%	7
Austria	3,8%	7
Belgium	0,5%	1
Canada	0,5%	1
Croatia	2,2%	4
Denmark	4,3%	8
Czech Republic	1,6%	3
Finland	1,6%	3
France	1,1%	2
Germany	8,7%	16
Greece	2,2%	4
Hungary	1,6%	3
Ireland	1,6%	3

Italy	11,4%	21
The Netherlands	4,9%	9
Norway	2,7%	5
Poland	4,3%	8
Portugal	3,8%	7
Romania	11,4%	21
Slovakia	0,5%	1
Slovenia	3,2%	6
Spain	4,9%	9
Sweden	1,6%	3
Switzerland	3,2%	6
Turkey	1,1%	2
United Kingdom	3,2%	6
USA	2,7%	5
Other	7,6%	14

The majority of replies came from pathologists working in university clinics or academic hospitals (61.3%, n=111), followed by respondents from community hospitals (28.2 %, n=51) and private healthcare institutions (10.5%, n=19). Survey participants represented board certified pathologists with more than ten or less than ten years of experience in 65.8%, (n=121) and in 23.4% (n=43), respectively. The remaining 10.9% (n=20) of the survey participants were residents.

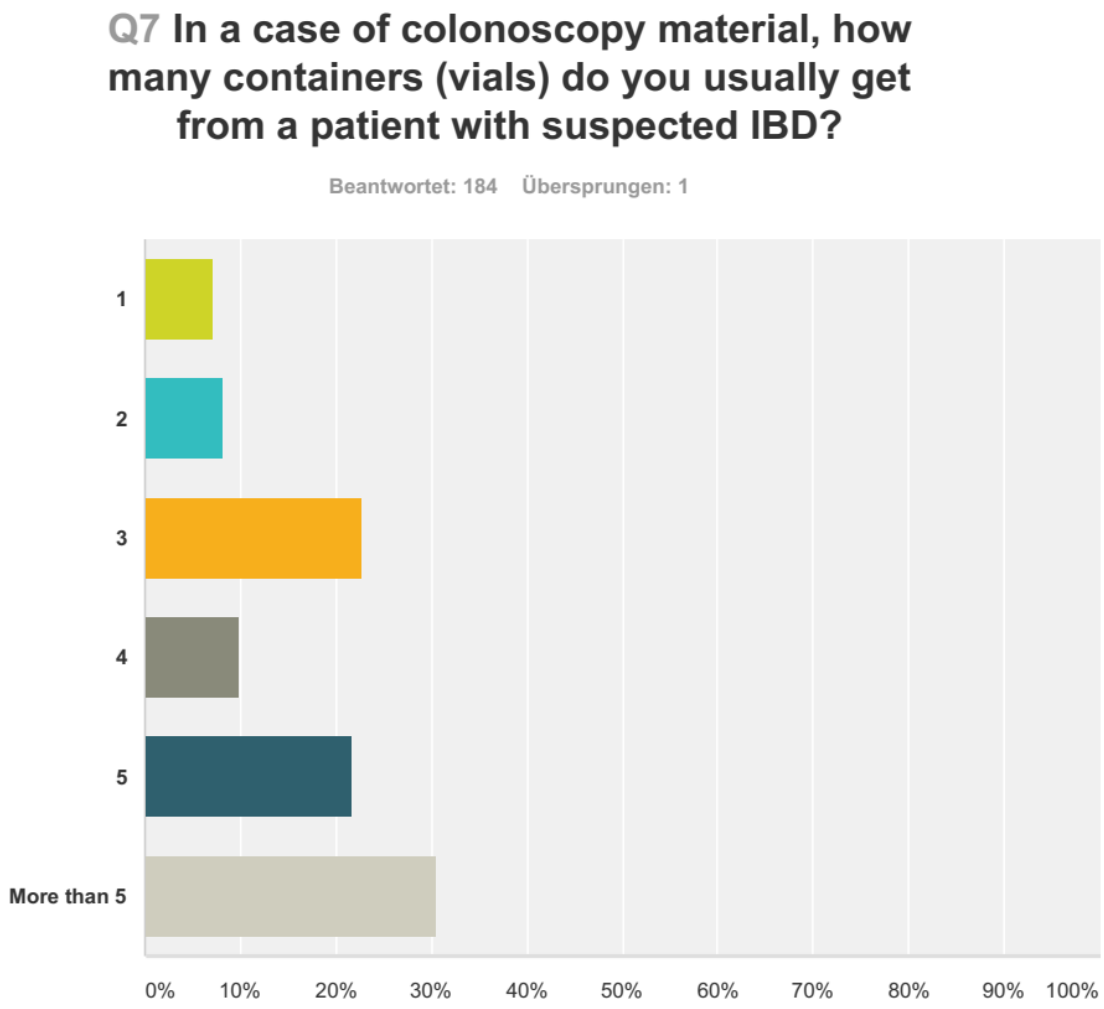
Nearly all participants (94.4%, n=170) were members of ENGIP, 55.6% (n=100) claimed membership of the European Society of Pathology (ESP) and 47.8% (n=86) of the International Academy of Pathology (IAP).

All pathologists (100%, n=185) investigated biopsies and 89.2% (n=165) dealt with resection specimens from IBD-patients.

Received biopsy material (Q6-Q13, Q19)

In case of biopsy material from colonoscopy in patients with suspected IBD, the vast majority of the respondents (91.2%, n=166) received biopsy material from different anatomic locations in separate tissue containers. In a minority of cases (8.8%, n=16) the entire biopsy material was usually submitted in one single container.

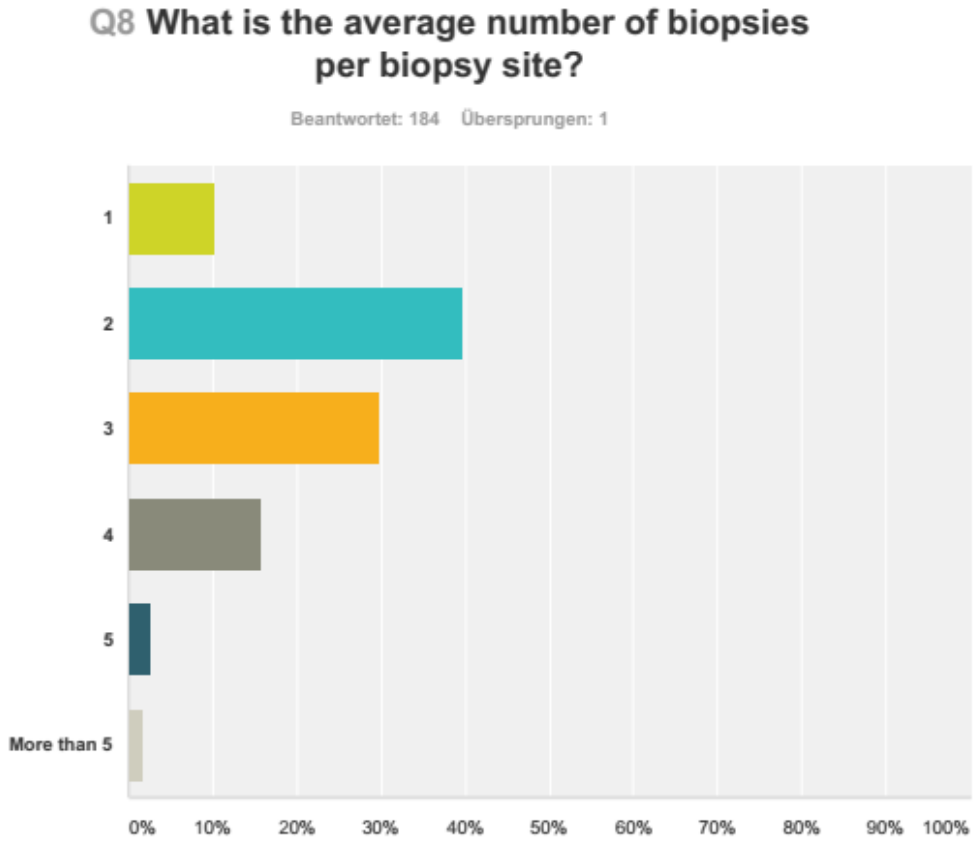
The number of submitted tissue containers with biopsy material after colonoscopy in patients with suspected IBD was individual, as seen in Figure 3. Most frequently, participants got more than five tissue containers (30.4%, n=56), followed by three and five in 22.8% (n=42) and 21.7% (n=40), respectively. Four containers were submitted in 9.8% (n=18) of the cases, two containers in 8.2% (n=15) and one container in 7.1% (n=13).



Antwortoptionen	Beantwortungen	
1	7,07%	13
2	8,15%	15
3	22,83%	42
4	9,78%	18
5	21,74%	40
More than 5	30,43%	56
Gesamt		184

Figure 3: ENGIP Survey: Number of containers from colonoscopy

The number of biopsies per site also showed a certain degree of variety (Figure 4). Most frequently, respondents received two biopsies per anatomic site (39.7%, n=73), followed by three in 29.9% (n=55) and four biopsies in 15.8% (n=29) of the cases. One biopsy per site was submitted in 10.3% (n=19) of the cases. Sampling five or more than five biopsies per anatomic site was rare (in 2.7%, n=5 and 1.6%, n=3, respectively).



Antwortoptionen	Beantwortungen	
1	10,33%	19
2	39,67%	73
3	29,89%	55
4	15,76%	29
5	2,72%	5
More than 5	1,63%	3
Gesamt		184

Figure 4: ENGIP Survey: Average number of biopsies per site

The majority of respondents (88.5%, n=162) considered the location of the biopsy material mostly and 9.9% (n=18) sometimes as clearly indicated. According to very few pathologists (1.7%; n=3) clinicians did not sufficiently indicate the topographic origin of the biopsies.

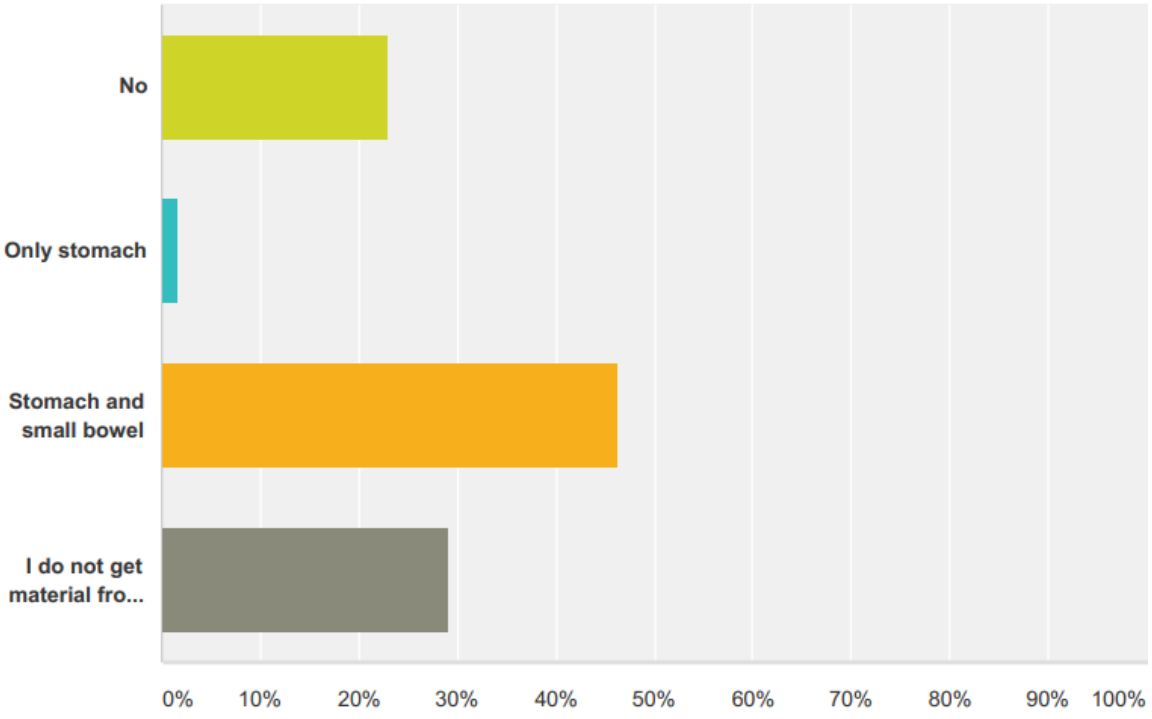
Separate collection of rectal biopsies was common practice: Most of the pathologists (79%, n=143) received rectal biopsies in the majority of the cases in a separate container and 16.0% (n=29) sometimes. Only few pathologists (5.0%, n=9) usually did not receive rectal biopsies in a separate tissue container.

Biopsy material from the terminal ileum was regularly provided in suspected IBD: In 77.5% (n=141) in most of the cases and in 20.9% (n=38) sometimes. A minority of pathologists (1.7%, n=3) did not receive biopsies from the terminal ileum from patients with presumed IBD.

Practice of sampling the upper Gastrointestinal Tract (GIT) in children/adolescent patients is showed in Figure 5: When IBD is suspected in pediatric or adolescent patients, stomach and the small bowel were biopsied in 46.5% (n=85) and in very few cases only the stomach (1.6%, n=3). The remaining respondents either were not provided with biopsy material from the upper GIT when IBD is suspected in pediatric / adolescent patients (23.0%, n=42) or did generally not receive material from this patient group (29.0%, n=53).

Q12 Do you usually get biopsy material from the upper gastrointestinal tract from a paediatric / adolescent patient with suspected IBD?

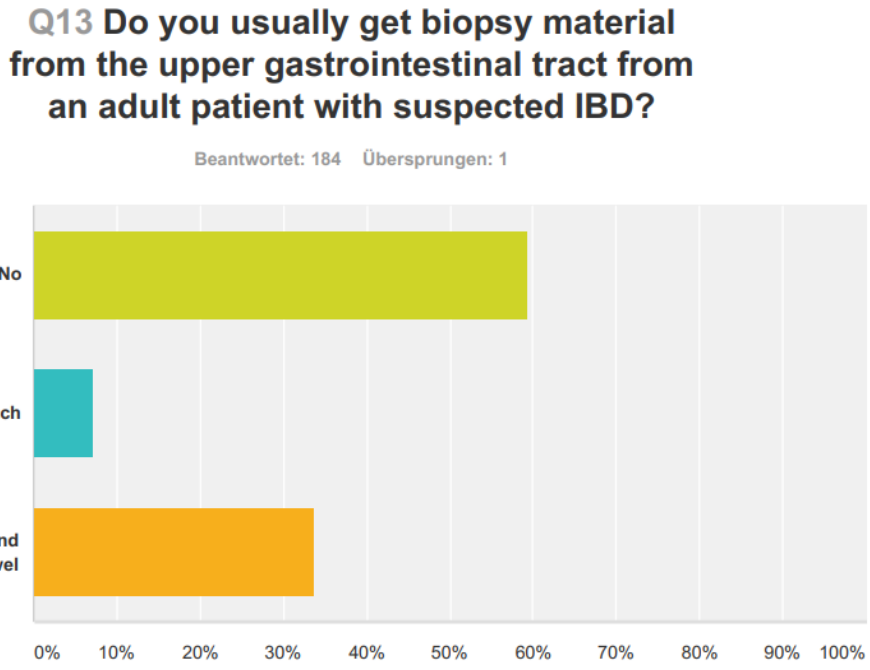
Beantwortet: 183 Übersprungen: 2



Antwortoptionen	Beantwortungen	
No	22,95%	42
Only stomach	1,64%	3
Stomach and small bowel	46,45%	85
I do not get material from paediatric / adolescent patients	28,96%	53
Gesamt		183

Figure 5: ENGIP Survey: Sampling of the upper GIT in children/adolescents

When IBD is suspected in adult patients, 59.2% (n=109) of the pathologists did not receive biopsies from the upper GI tract, whereas 33.7% (n=62) were provided with biopsies from both the stomach and the small bowel. Solely stomach biopsies were seldom submitted (7.1%, n=13) when IBD is suspected in adults (Figure 6).



Antwortoptionen	Beantwortungen	
No	59,24%	109
Only stomach	7,07%	13
Stomach and small bowel	33,70%	62
Gesamt		184

Figure 6: ENGIP Survey: Sampling of the upper GIT in adolescent patients

The size of the samples was considered widely as sufficient among the respondents. The size was in 6.5% (n=12) always, in 83.7% (n=154) in most of the cases and in 8.7% (n=16) sometimes regarded as adequate. For merely 1.1% (n=2) of the pathologists the size of the samples was usually not sufficient.

Provided clinical information (Q14-Q18)

Clinicians submitted patient related information along with biopsy material to the pathologists very inconsistently. Table 3 gives an overview over the frequency of reported clinical data. Patient's age was always reported in 96.7%, (n=178), and in the majority of cases in 2.7% (n=5). Only one participant (0.5%) sometimes received information about the patient's age.

Information about endoscopic findings was quite consistently communicated to the pathologists, in 35.0% (n=64) always, in 43.7% (n=80) in most of the cases and in 19.7% (n=36) sometimes. Very few pathologists (1.6%, n=3) missed information about endoscopic findings along with biopsy material.

Duration of the patient's symptoms was less commonly provided: In 9.3% (n=17) always, in 37.7% (n=69) in the majority of the cases and in 41.5% (n=76) sometimes. Some participants (11.5%, n=21) generally did not receive information about the patient's duration of symptoms.

The patient's treatment history and immune status were scarcely reported by the clinicians. Merely 5.0% (n=9) of the respondents were always informed about treatment history and 25.3% (n=46) in the majority of the cases. Most of the pathologists (53.3% n=97), replied that treatment history was only sometimes provided. Some of the participants (16.5%, n=30) generally missed information about prior treatment.

Patient's immune status was most seldomly reported. Results showed that information about the immune status was always given in 2.2% (n=4), in the majority of the cases in 8.2% (n=15), sometimes in 51.9% (n=95) and in 37.7 % (n=69) not at all.

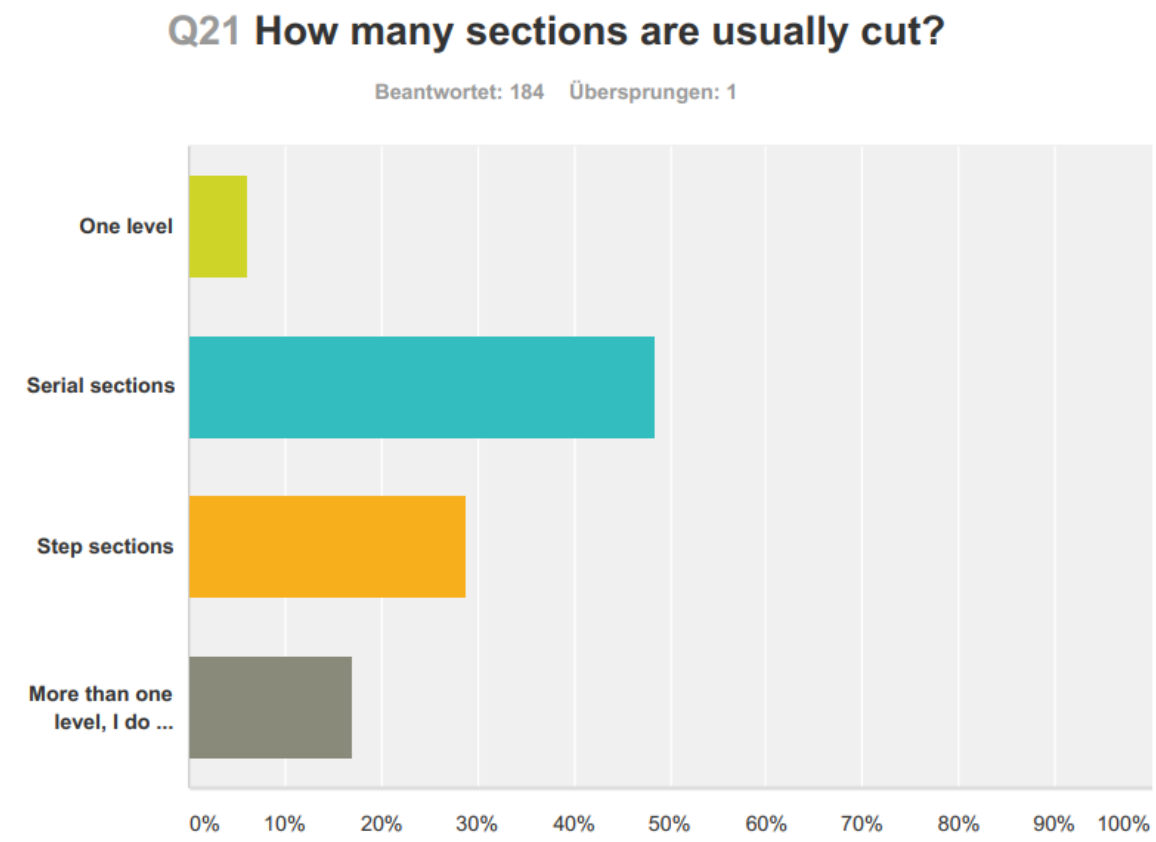
Table 3: Reported clinical information by clinicians

	Patient's age	Endoscopic findings	Duration of Symptoms	History of treatment	Immune status
Always reported	96.7%, n=178	35.0%, n=64	9.3%, n=17	4.6%, n=9	2.2%, n=4
Reported in the majority of cases	2.7%, n=5	43.7%, n=80	37.7%, n=69	25.3%, n=46	8.2%, n=15
Sometimes reported	0.5%, n=1	19.7%, n=36	41.5%, n=76	50.3%, n=97	51.9%, n=95
Not reported	0.0%, n=0	1.64%, n=3	11.48%, n=21	16.48%, n=30	37.7%, n=69

Laboratory handling of tissue samples (Q20-Q22)

The survey revealed varying results concerning some aspects of handling tissue material by the laboratory technicians. In 50.5% of the cases (n=93) tissue specimens were oriented during the embedding procedure whereas in 42.9% (n=79) tissue samples were not oriented. Some of the participants (6.5%, n=12) did not know whether the laboratory technicians orient the tissue material or not.

Sectioning methods were also heterogenous, as seen in in Figure 7. Most common practice was cutting serial sections (48.4%, n=89). In 28.8% (n=53) of the cases the technicians cut step sections. Some respondents (16.9%, n=31) did not know whether they were provided serial or step sections but received at least more than one level cut from the paraffin block. One tissue level was cut in 6.0% (n=11) of the cases.



Antwortoptionen	Beantwortungen	
One level	5,98%	11
Serial sections	48,37%	89
Step sections	28,80%	53
More than one level, I do not know whether serial or step sections	16,85%	31
Gesamt		184

Figure 7: ENGIP Survey: Sectioning methods

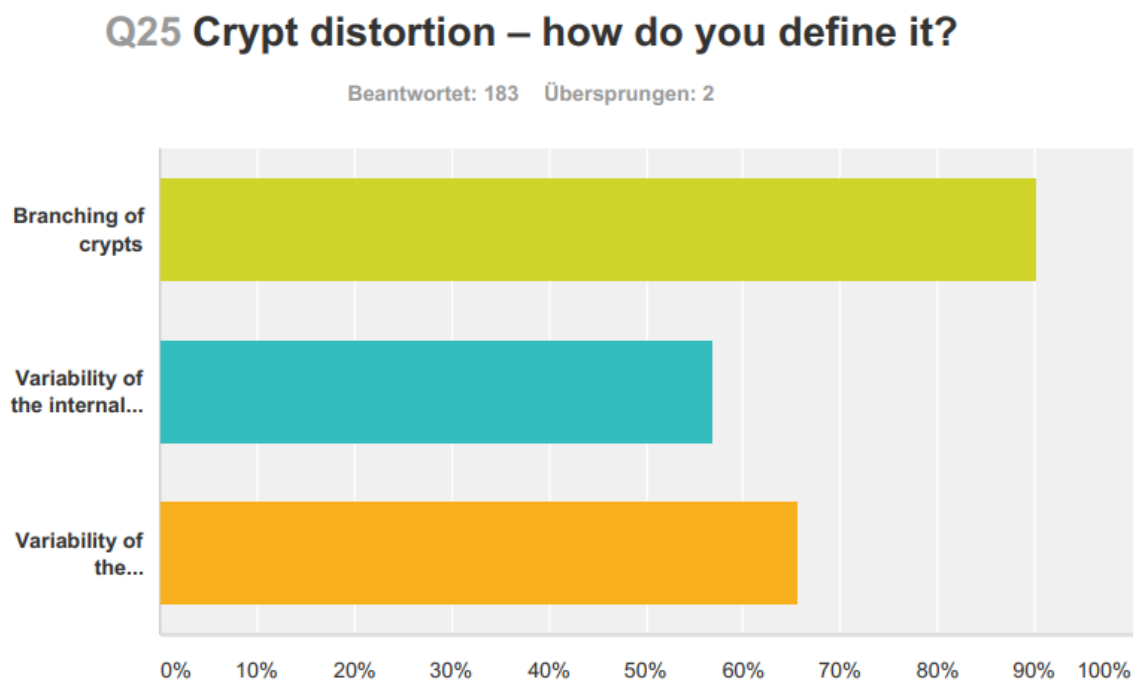
Hematoxylin-Eosin (H&E) was the most frequently applied staining for histologic diagnosis of IBD. In 74.3% (n=136) of the cases only H&E was applied for IBD diagnosis in daily practice whereas 22.4% (n=41) of the pathologists tended to use histochemical stainings like Periodic acid–Schiff (PAS) or Giemsa additional to H&E and very few participants (3.3%; n=6) used to apply immunohistochemistry (e.g.CD68) supplementary to the H&E stain.

Theoretical knowledge and practical approach to histologic diagnosis of IBD (Q23-Q55)

Upon microscopy, architectural changes of the mucosa were assessed by almost every participant (95.6% n=175) by examining the crypts whereas 61.2% (n=112) of the pathologists evaluated changes of the mucosal architecture by looking at the appearance of the mucosal surface.

Survey results showed varying opinions about the histologic phenomenon “villiform change” of the mucosal surface among the participants. According to 34.3% (n=61) it is a result of widened crypts, 32.0% (n=57) denied this assertion and the remaining third of the pathologists (33.7%, n=60) did not know whether villiform change is the result of crypt widening or not.

Survey results showed some degree of variance among participants concerning the definition of crypt distortion as shown in Figure 8. Most pathologists (90.2%, n=165) agreed that crypt distortion is defined as branching of crypts, less participants defined distorted crypts as a variability in intercryptal distance (65.6%, n=120) or as a variability of the internal diameter (56.8%, n=104).



Antwortoptionen	Beantwortungen	
Branching of crypts	**90,16%**	165
Variability of the internal diameter	**56,83%**	104
Variability of the intercryptal distance	**65,57%**	120
Befragte gesamt: 183		

Figure 8: ENGIP Survey: Definition of crypt distortion

In further specifying the minimum number of crypts involved to make the definite diagnosis of crypt distortion at a microscopical level the participants set different cut-offs: More than half of the participants (57.7%; n=105), diagnosed crypt distortion, if more than two out of ten crypts are involved, 28.6% (n=52) set the cut-off level at two out of ten distorted crypts and for 13.7% (n=25) of the respondents less than two out of ten distorted crypts sufficed for the diagnosis of crypt distortion.

When defining the term “crypt atrophy”, 72.5% of the participants (n=132) considered crypt shortening as a feature of atrophy and 69.8% (n=127) defined crypt atrophy as a loss of crypts.

The definition of the term “colitis” varied among participants. For the majority of the respondents (65.6%, n=120) both criteria, epithelial abnormalities and increased number of inflammatory cells must be present for the definition of colitis. One third of the participants (33,3%, n=61) defined colitis as an increased number of inflammatory cells. Merely 1.1% of the respondents (n=2) required solely the presence of epithelial abnormalities for the definition of colitis.

There was wide agreement on the definition of the term “chronic colitis”. The majority (79.9%, n=147) of responding pathologists required the following three criteria to be present: Architectural abnormalities, increased mononuclear inflammatory cells and basal inflammatory cells. The presence of solely architectural abnormalities was considered by 10.9% (n=20) of the respondents as single necessary criterion. Few pathologists (6.0%, n=11) predicated the definition of chronic colitis solely on the presence of increased number of mononuclear inflammatory cells or solely on the occurrence of basal inflammatory cells (3.26%, n=6).

Most of the respondents (89.0%, n=162) agreed quite unanimously that the presence of granulomas is a helpful diagnostic indicator for CD. Some respondents (6.6%, n=12) required the presence of granulomas for diagnosis of CD in any case. Few pathologists (2.2%, n=4) regarded granulomas as sufficient or as irrelevant for the diagnosis of CD, respectively.

There was wide consent among the pathologists that the finding of terminal ileitis is helpful for establishing the diagnosis of CD (82.1%; n=151). The opinions of the remaining participants were quite equally distributed: terminal ileitis was considered in 6.0% (n=11) as necessary, in 7.1% (n=13) as sufficient and in 4.9% (n=9) as irrelevant for the diagnosis of suspected CD.

Survey participants disagreed on the diagnostic value of focally enhanced gastritis (FEG) in suspected IBD. FEG has been considered by 47.8% (n=87) as a helpful finding for the diagnosis CD. Few pathologists (2.2%, n=4) regarded this finding as helpful for diagnosing UC. According to 28.0% (n=51) FEG is a helpful finding for the diagnosis of both UC and CD. In 22.0% (n=40) of the cases responding pathologists did not see any diagnostic value in FEG in suspected IBD.

Interpretation of the inflammatory infiltrate for differentiating IBD histologically from other forms of colitis seemed to vary according to survey results. The distribution of inflammatory cells was considered by the majority of the respondents (92.9%, n=171) as a helpful parameter. The composition of inflammatory cells was regarded in 67.4% (n=124) and its density in 37.5% (n=69) of the cases as useful for considering other inflammatory differentials of IBD.

Regarding the definition of “basal distribution” of inflammatory cells, 69.4% (n=127) of the pathologists replied that this term is defined as “presence of inflammatory cells located between the crypt base and the lamina muscularis mucosae”. The remaining 30.6% (n=56) approved the looser definition of the term: “Inflammatory cells being distributed in the lower third of the lamina propria”.

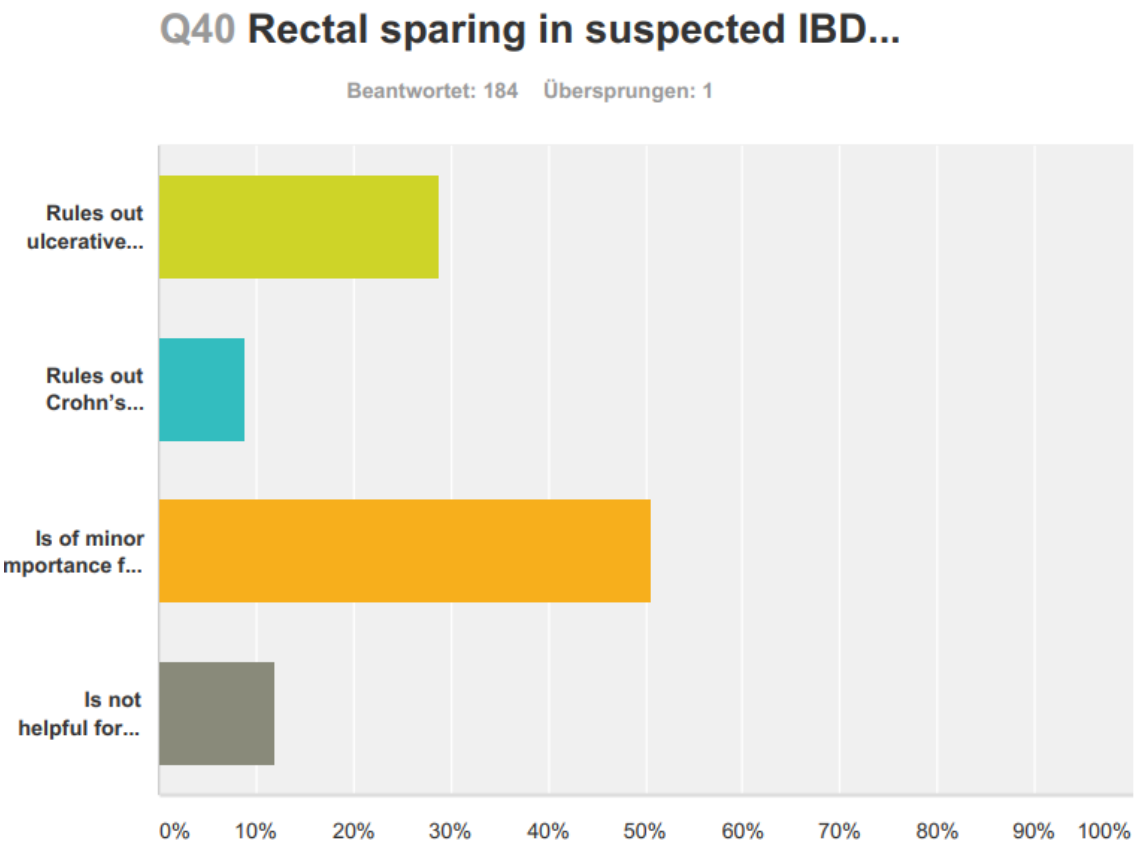
Interpretation of terms describing the distribution of inflammatory infiltrate showed varying opinions. The term “diffuse (continuous)” inflammation was defined by 86.8% (n=158) as inflammatory infiltrate in the same density being present in different samples (from different sites) and by 42.9% (n=78) as same density in one single biopsy. The term “focal (discontinuous)” inflammation has been defined by 81.3% (n=148) as being of variable density in different samples (from different sites) and by 63.2% (n=115) as inflammation with variable density in one single biopsy.

The terms “focal” and “patchy” were a matter of disagreement among the respondents. Approximately half of the pathologists (53.3%, n=98) made a distinction between the two terms, the remaining respondents (46.7%, n=86) considered both terms as synonymous.

More participants (69.4%, n=127) considered the right colon as the prevailing location of colonic CD rather than both sites equally (27.9%, n=51) or the left colonic side (2.7%, n=5).

The left colon has been presumed to be the prevailing location of UC according to most survey participants (92.9%; n=170). The remaining minority regarded the right colon or both sides as equally affected, in 1.6% (n=3) and in 5.5% (n=10), respectively.

The phenomenon of rectal sparing in suspected IBD was construed differently as showed in Figure 9. Half of the participants (50.5%, n=93) attributed minor importance of rectal sparing for diagnosis of IBD. According to 28.8% (n=53) of the respondents rectal sparing rules out UC whereas 8.7% (n=16) regarded rectal sparing as exclusion criterion for CD. The remaining 12.0% (n=22) did not see any diagnostic help in assessing rectal sparing in suspected IBD.



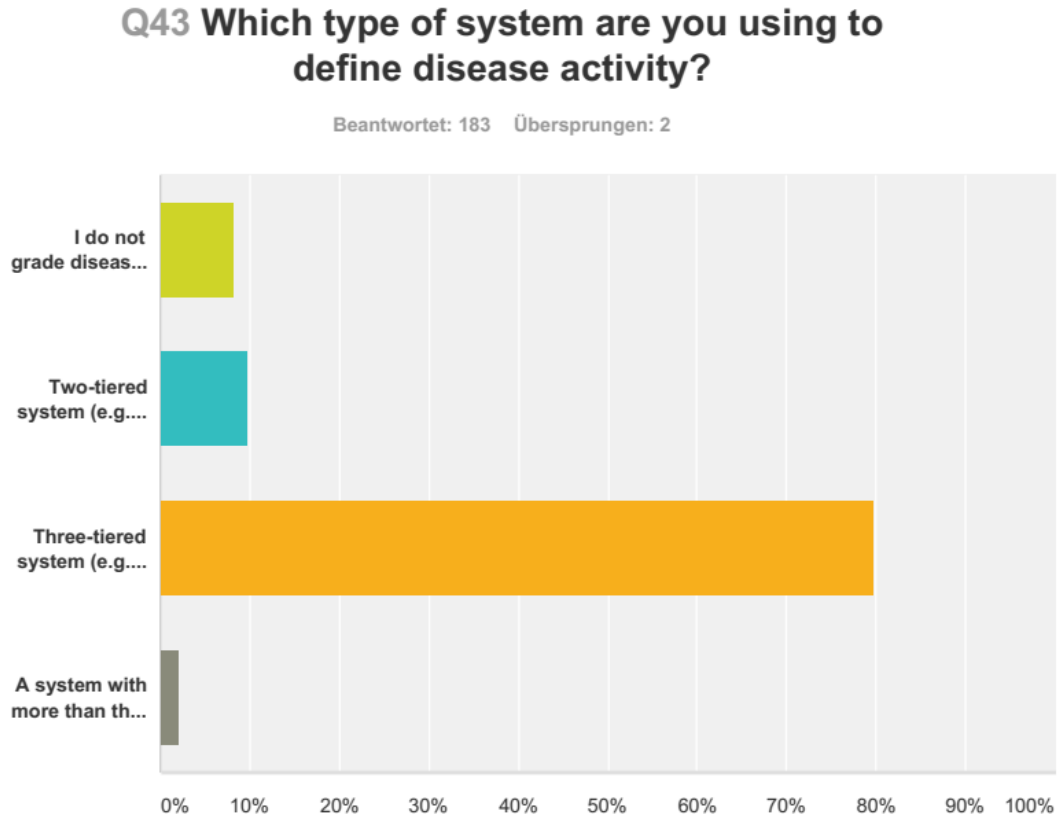
Antwortoptionen	Beantwortungen	
Rules out ulcerative colitis	28,80%	53
Rules out Crohn's disease	8,70%	16
Is of minor importance for diagnosis	50,54%	93
Is not helpful for diagnosis	11,96%	22
Gesamt		184

Figure 9: ENGIP Survey: Interpretation of rectal sparing

Histologic assessment of disease activity in UC was performed by almost all pathologists (94%, n=172). The remaining minority (6.0%, n=11) usually did not assess inflammatory activity in UC.

In CD, participants also commonly assessed disease activity (78.0%, n=142). The remaining 22.0% (n=40) usually did not evaluate inflammatory activity in CD.

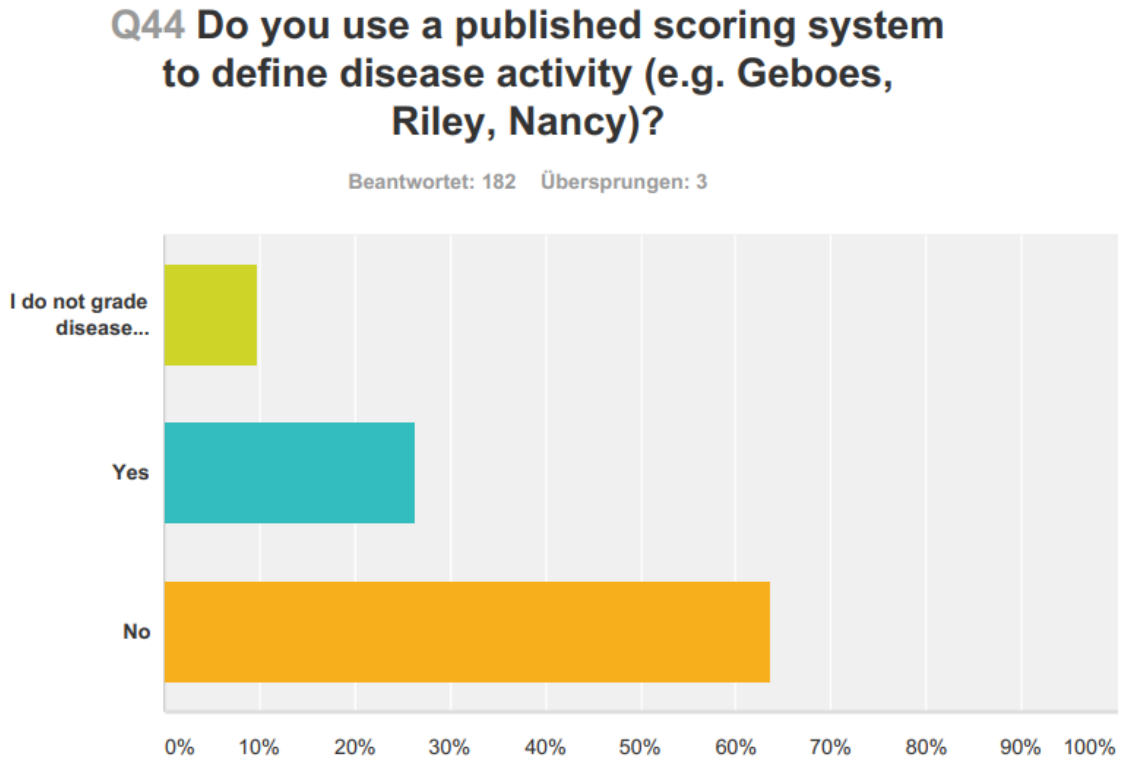
A three-tiered system for grading disease activity (e.g., with a range from mild to moderate up to severe) has been adopted by most of the participating pathologists (79.8%, n=146). A two tired system (with e.g., a low and high grade) was generally applied by 9.8% (n=18). A grading system with more than three grades was rarely used (2.2%, n=4). The remaining 8.2% (n=15) did not grade disease activity (Figure 10).



Antwortoptionen	Beantwortungen	
I do not grade disease activity	8,20%	15
Two-tiered system (e.g. low versus high grade)	9,84%	18
Three-tiered system (e.g. mild, moderate, severe)	79,78%	146
A system with more than three grades	2,19%	4
Gesamt		183

Figure 10: ENGIP Survey: Grading systems for disease activity

Apart from the 9.9 % (n=18) of the respondents who did not grade disease activity, 26.4% (n=48) of the pathologists usually applied officially published scoring systems (e.g., Geboes, Nancy-Index, or Riley), whereas 63.7% (n=116) did not use an officially published scoring system to grade disease activity in IBD (Figure 11).



Antwortoptionen	Beantwortungen	
I do not grade disease activity	9,89%	18
Yes	26,37%	48
No	63,74%	116
Gesamt		182

Figure 11: ENGIP Survey: Grading of Activity

Table 4 details how pathologists interpreted several histologic features of disease activity. Many survey participants agreed that the presence (81.8%, n=148) and the location (77.0%, n=137), of neutrophilic granulocytes are major features for assessing disease activity. Some pathologists (12.9%, n=23) regarded the location of neutrophilic granulocytes and few (5.5%, n=10) their presence as a minor feature for assessing disease activity. According to some pathologists the presence (11.6%, n=21) or the location (7.9%, n=14) of neutrophils were the only important features in active disease. Merely a few participants regarded the presence (1.1%, n=2) and location (2.3%, n=4) of neutrophilic granulocytes as irrelevant for the evaluation of disease activity.

Most of the participants (85.0%, n=153) agreed that mucosal breaks like erosions or ulcerations are a major hallmark of disease activity whereas 12.8% (n=23) valued mucosal breaks as a minor feature. A few respondents (2.2%; n=4) considered mucosal breaks as the only feature of importance when evaluating disease activity.

Other forms of mucosal abnormalities like regenerating or recovering epithelium was according to 56.6% of the pathologists (n=103) a minor feature for assessing activity, 29.7% (n=54) regarded them is a major feature, and the remaining respondents replied that regenerating mucosal alterations are either the only important feature (12.6%; n=23) or not relevant (1.1%; n=2) for measuring activity.

Table 4: Interpretation of histologic features of activity

	Presence of neutrophils	Location of neutrophils	Mucosal breaks (Erosion, ulceration)	Regenerating or recovering epithelium
The only important feature	11.6%, n=21	7.9%, n=14	2.2%, n=4	12.6%; n=23
Major feature	81.8%, n=148	77.0%, n=137	85.0%, n=153	29.7%, n=54
Minor Feature	5.5%, n=10	12.9%, n=23	12.7%, n=23	56.6%, n=103
Not important	1.1%, n=2	2.3%, n=4	0.0%, n=0	1.1%; n=2

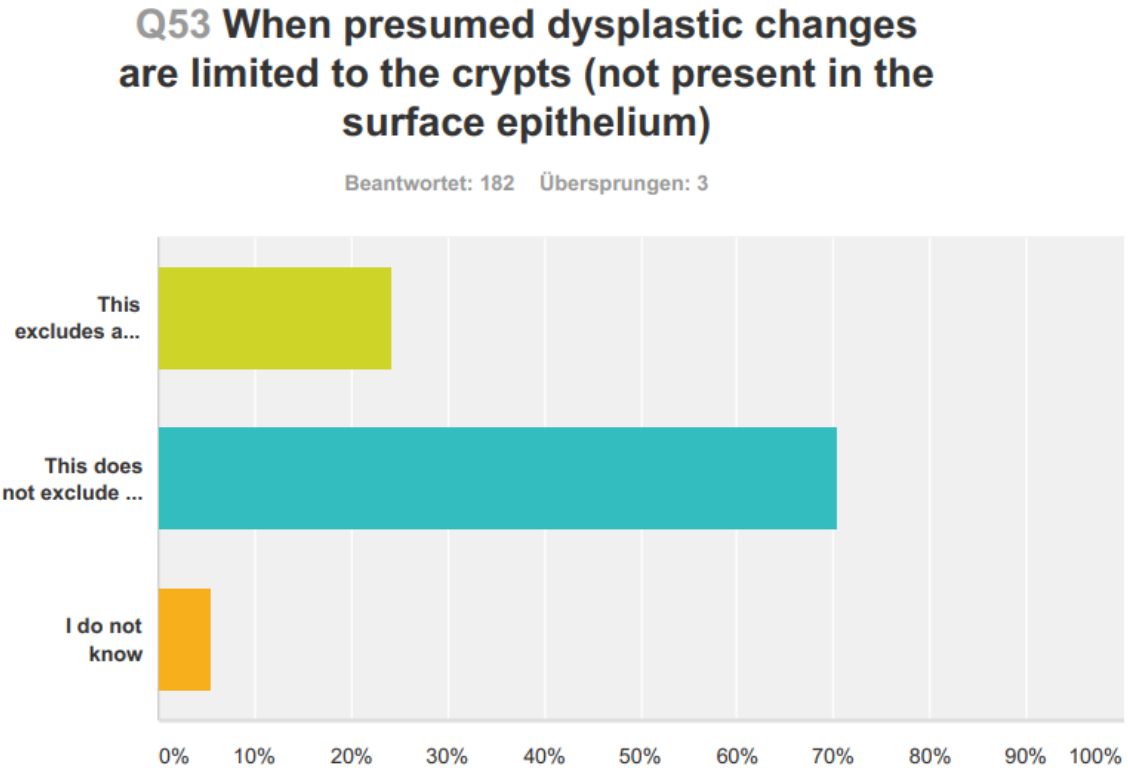
Almost every pathologist usually graded dysplasia (98.9%; n=179). The remaining 1.1% (n=2) usually did not perform any grading of dysplasia.

A two-tiered system for grading dysplasia (e.g., low- and high-grade dysplasia) was most widely favored (91.2%, n=165), whereas 7.7 % (n=14) applied a system with three different ascending grades (e.g., low-, moderate-, and high-grade dysplasia). The remaining 1.1 % (n=2) usually did not grade dysplasia at all.

A differentiation between colitis-associated and sporadic (colitis-independent) dysplasia was performed in most of the cases (78.1 %, n=143), whereas 21.9 % (n=40) did not distinguish between those two forms of dysplasia.

Surface maturation was clearly seen as a regenerative process by almost every pathologist (98.4%, n=179). The remaining 4.4% (n=8) interpreted maturation of the surface epithelium a feature of dysplasia.

According to the majority of pathologists (70.3%, n=128) the finding of crypt restricted dysplastic changes (without involving the surface epithelium) is not an exclusion criterion for diagnosis of definite dysplasia. Nearly one fourth (24.2%, n=44) of the pathologists, however, would not have diagnosed dysplasia if they had observed crypt limited dysplastic changes. The remaining 5.5% (n=10) did not know how to interpret dysplastic changes limited to the crypts for the final diagnosis of dysplasia (Figure 12).



Antwortoptionen	Beantwortungen	
This excludes a diagnosis of dysplasia	24,18%	44
This does not exclude a diagnosis of dysplasia	70,33%	128
I do not know	5,49%	10
Gesamt		182

Figure 12: ENGIP Survey: Interpretation of dysplastic changes limited to the crypts

Practice of applying immunohistochemistry for assessing dysplastic lesions has been heterogeneous as shown in Table 5: P53 immunochemistry for evaluating suspicious dysplasia was used infrequently: Always by 11.6% (n=21), in the majority of cases by 12.2% (n=22) and sometimes by 49.2% (n=89). P53 immunochemistry was never used by 27.1% (n=49) of the respondents. MIB-1/Ki67 immunochemistry was less commonly applied than P53 for evaluation of lesions suspicious for dysplasia: A small percentage (7.7%; n=14) always or mostly applied MIB-1/Ki67 immunochemistry, respectively, and almost half of the respondents (46.2%, n=84) used it sometimes. The remaining 38.5 % (n=70) of the pathologists never applied MIB-1/Ki67 immunochemistry in cases with suspected dysplasia.

Table 5: Use of P53 and Ki67/MIB immunohistochemistry for assessment of dysplasia

	Always used	**Used in the majority of the cases**	**Sometimes used**	**Never used**
P53	11.6%, n=21	12.2%, n=22	49.2%, n=89	27.1%, n=49
Ki67/MIB	7.7%, n=14	7.7%, n=14	46.2%, n=84	38.5 %, n=70

Macroscopic workup of IBD resection specimens (Q56-Q60)

Photographic documentation of resection specimens from patients with IBD was heterogeneous: While performing gross examination, 55.9% (n=100) of the pathologists usually took photos of the specimen while the remaining 44.1% (n=79) did not perform photographic documentation.

Strict recommendations or rules for tissue sampling and macroscopic workup by their institution must have been followed in 62.98% (n=114) of the cases. According to 37.0% of the respondents (n=67) no strict rules of tissue sampling from their respective pathologic institutions had to be adhered to.

When sampling inflamed mucosa in resection specimens with IBD, 1.7 % of the pathologists (n=3) only sampled inflamed mucosa if it is suspicious for dysplasia or cancer. If there was no suspicion of dysplasia or cancer solely one or two probes for diagnostic confirmation were taken only by few pathologists (7.2%, n=13). Half of the participants (50.8%, n=92) usually sampled inflamed mucosa with one probe every 10 cm without suspicion of dysplasia cancer and 40.3% (n=73) every 5 cm or closer.

Macroscopically normal mucosa (other than resection margins) of resection specimens from IBD patients was always sampled by most of the pathologists (88.3%, n=159), sometimes by 10.0 % (n=18) and never by few pathologists (1.67%, n=3).

When dealing with resection specimens with IBD-associated carcinoma, the majority of pathologists (88.4%, n=160) always sampled macroscopically inflamed mucosa located in a remote area of the tumor to detect or rule out synchronous dysplasia, whereas 11.1% (n=20) sometimes sampled those areas. One participant (0,6%, n=1) replied never to sample inflamed mucosa in a distant area from a tumor.

4 Discussion

ECCO and the ESP have published guidelines and consensus papers providing evidence-based standards for diagnosis and reporting of IBD (109), (126), (133), (134). However, little is known about the pathologist's current routine practice in IBD diagnosis and adherence to guidelines across Europe. Study results revealed agreement as well controversy on certain issues as well as differences and commonalities in pathologic practice. The issues showing wide disagreement often reflected the lack of clear definitions or matters of controversies in current guidelines. Clinician's practice of submitting biopsy material to the pathologists showed considerable variation.

Personal information

The ENGIP-questionnaire was completed by 185 participants from 36 different countries and represents the current practice of pathologists in the field of IBD throughout Europe. Most replies came from Germany, Romania, and Italy. Participants were from all educational levels (residents and board-certified pathologists) and institutions (university clinics, public hospitals, and private institutions). More than half of the respondents were represented by bord certified and experienced pathologists and by pathologists from academic institutions, respectively. Nearly everybody claimed ENGIP membership. Members of IAP or ESP were also frequent. Every pathologist was examining biopsies and most of them were also dealing with resection specimens from suspected or confirmed IBD patients.

Received biopsy material

Histological examination of endoscopic biopsy specimens is an important element in establishing the diagnosis of IBD (98). Biopsy evaluation by the pathologist depends somewhat on proper sampling in colonoscopy and appropriate labeling of the biopsy origins by the clinicians. Sufficient biopsy sampling bears high diagnostic value and improves assessment of disease extent, classification of IBD and treatment effects for the respective areas by the pathologist. (131), (136). By inadequate inconsequent separation and labeling the pathologist may not be able to interpret discontinuous distribution pattern in UC and skip lesions of CD properly which may hamper the distinction between CD and UC (98), (131). Therefore, international guidelines from ECCO, ESP and BSG recommend the endoscopist to perform systematic multi-segment biopsy sampling of the ileocolon. Additionally, certain standards of biopsy handling should be followed. Specifically, acquisition of at least two segmental biopsies from five sites of the colorectum and the terminal ileum is recommended in the initial diagnostic process. Biopsies should be collected in separate tissue containers to allow anatomic correlation of the biopsy site. Obtaining sufficient amount of clearly labeled biopsies in the first endoscopy in suspected IBD patients is crucial for accurate diagnosis, assessment of disease distribution and severity (109), (126), (135), (137), (138). The biopsy sites in the colorectum should include the ascending, transverse, descending, and sigmoid colon as well as the rectum (131), (139).

The majority of pathologists usually received biopsy material from colonoscopy of patients with suspected IBD in separate containers and mostly considered their origin as clearly indicated. Specifically, rectal biopsies were also frequently submitted in separate containers by the clinicians.

However, the clinician’s sampling techniques seemed to be considerably individual, referring to the number of submitted tissue containers and the number of biopsies per site: When following the standard biopsy protocol according to guidelines by collecting the samples from the required six biopsy sites separately, the pathologist should receive at least six different containers (each representing one biopsy site). The ideal number of more than five containers was merely reached in 30.4%. Five containers were submitted in 21.7%. In the remaining cases, one to four containers were submitted.

Conclusively, the ideal number of different containers is often not submitted and is very individual. However, the questionnaire did not clarify whether the clinicians did not sample the recommended six different biopsy sites consequently or whether adequate collection of biopsies in separate containers respective to their exact origin was not carried out properly.

On the other hand, clinicians mostly followed the guideline recommendations of taking a minimum of two biopsies per anatomic site since 89.7% of the pathologists were provided with two or more biopsies per site. Also in this issue, the number of submitted biopsies showed a certain degree of variation with two biopsies per site being the most common amount, followed by three and four.

IBD frequently shows affection of the terminal ileum either as terminal ileitis in CD or as backwash ileitis in UC (58). Obtaining ileal biopsies is not only valuable for the establishment of IBD diagnosis but also for distinguishing backwash ileitis in UC from terminal ileitis in CD on a histological level (140). Biopsies from terminal ileum were frequently provided to the pathologists (in 77.5% in the majority of cases). Therefore, clinicians seemed to recognize the diagnostic importance of ileoscopy in suspected IBD patients.

Up to 30% of IBD patients are diagnosed under 20 years of age (141). Guidelines of the IBD Working Group of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) require complete endoscopic examination of the upper and lower gastrointestinal tract (including duodenal biopsies) in children and adolescent patients for the diagnosis of IBD regardless of upper GI symptoms (142), (143), (144), (145).

The recommendations of submitting stomach and small bowel biopsies in pediatric /adolescent patients for initial diagnosis were met in 46.5% of the cases. It must be considered however, that almost 29.0% of the participating pathologists did not examine pediatric tissue at all. Endoscopy of the upper GIT in adult IBD patients may be useful for assessing exact disease distribution or adapting treatment regimen. Furthermore, it may be beneficial for patients with upper abdominal symptoms (vomiting, abdominal pain, dyspepsia).

Routine upper endoscopy for initial diagnosis of IBD in asymptomatic IBD patients is not recommended in the guidelines and still remains a matter of controversy (134), (139). One third (33.7%) of the pathologists, however, was provided with stomach and small bowel biopsies in the initial diagnosis of IBD in adult patients. Stomach and small bowel biopsies were more frequently submitted in pediatric than in adult patient group (46.5% vs. 33.7%). Solely stomach biopsies were seldom submitted in both pediatric and adult patient group (1.64% vs. 7.07%).

Provided clinical information

Insufficient clinical information may cause diagnostic difficulties to the pathologist in interpretation of histologic findings concerning differential diagnosis or evaluation of follow up examinations and eventually in drawing the correct clinicopathologic conclusions (98). Therefore, ECCO guidelines as well as the Erlangen International Consensus Conference on IBD strongly recommend the clinician to provide the following patient related information to the pathologist: Patient's age, symptoms and their duration as well as the previous treatment history regarding type and duration of therapy (109), (124), (131), (134), (135), (137).

Clinicians almost always reported patient's age to the pathologists (in 97.0% of the cases).

Communication of endoscopic findings, especially characteristic endoscopic lesions in UC and CD, severity and distribution of visible lesions and report of normally looking areas facilitates correct diagnosis of IBD on a microscopical level (98), (131), (140). Endoscopic findings were regularly reported by the clinicians, in 35.0% always and 43.7% in most cases.

Informing the pathologist about symptom duration is useful when considering other differentials like infectious colitis. In this case symptoms cease generally in less than one month whereas in IBD clinical symptoms may persist for a longer time before diagnosis (131). Furthermore, the report of symptoms without stating their duration may hamper the correlation of microscopic features of chronicity (98).

Clinicians communicated duration of symptoms (in 9.3% always and in mostly in 37.7%) less frequently than endoscopic findings and do not consequently adhere to the guidelines in this issue.

Effective medical treatment may induce microscopic improvement like decrease of inflammation and architectural abnormalities and may eventually lead to histological healing (130). Furthermore, patchiness of inflammation or rectal sparing are well-recognized treatment related effects in UC. Unawareness of previous treatment history may lead to misinterpretation and diagnostic difficulties in the discrimination between UC and CD (137), (146), (147). Information about previous treatment is valuable for evaluating its effects and the success of the current therapy in follow up investigations (131). Information about treatment history was sparsely reported as the survey results demonstrated: Half of the pathologists (53.3%) are merely sometimes informed about previous treatment and one forth (25.3%) in most cases. Report of treatment history, as recommended in current guidelines, is not consequently practiced by the clinicians.

CMV infection of the gastrointestinal tract is more likely to occur in immunocompromised patients rendering IBD patients at higher risk of developing CMV colitis (148), (149). It is recommended to search for CMV in patients with refractory disease after treatment with immunosuppressants (82), (99), (126). More than one third of the pathologists (37.7%) were not informed about the patient's immune status, 51.9% sometimes received a comment about patient's immune status. Only 10.4 % frequently are provided information about the patient's immune status. Information regarding the immune status of the patient is not standardly provided but is also not recommended in current ECCO guidelines (133), (134).

Conclusively, clinical reporting requires more consistency and adherence to the guidelines when sending in tissue material to pathologic institutions. Most frequently, clinicians reported patient age and endoscopic findings, followed by symptom duration, treatment history and immune status in a descending order.

Laboratory handling of tissue samples

Adequate size of the samples is important for accurate histological evaluation and is given when the entire mucosa and the lamina muscularis mucosae is present on the slide (107), (125). The majority of pathologists mostly considered the size of the samples as sufficient for histological analysis.

Propper assessment of certain microscopic features of IBD, especially basal plasmacytosis, crypt distortion and crypt shortening, necessitate adequate orientation of the biopsy specimens vertically to the mucosal surface prior to fixation (150), (151), (152). ECCO guidelines advise routine orientation of tissue samples in order to avoid transverse or tangentially cut sections which may hamper evaluation of histological features (126), (135). Laboratory technicians tended to orient tissue samples prior to embedding in about half of the cases. Orientation by the laboratory technicians is not uniformly practiced and should be carried out more consistently to improve diagnostic accuracy.

In step sections, one or more representative sections are cut from different tissue levels. In seral sections, continuous levels are cut from the specimen and are arrayed on multiple slides. In general, serial sections offer higher diagnostic precision than step sectioning, especially in assessing focal lesions (153), (154), (155). However, an optimal manner of sectioning in routine IBD diagnosis currently lacks standardization, since an exact requisite number of sections to be produced is not established yet. However, the expert panel from ECCO and ESP consider serial sectioning as a more accurate method for diagnosing IBD but recommend step sections for daily routine. Specifically, “two, or three tissue levels each consisting of five or more sections” (99), (126). According to survey results, sectioning showed some degree of variation with serial sections being most frequently produced (in 48.3%), followed by step sections in 28.8%. Cutting of just one level was very uncommon.

According to ECCO guidelines H&E staining alone is sufficient for histologic IBD diagnosis (99), (109), (126), (134), (135). Survey participants preferred to diagnose IBD solely on H&E staining, as recommended in the guidelines. Additional histochemical staining like PAS or Giemsa or immunochemistry like CD68 were not common practice.

Theoretical knowledge and approach to histologic diagnosis of IBD

One of the main histologic hallmarks of IBD are alterations in mucosal architecture which comprise pathologic changes of mucosal surface and crypt morphology (107), (125) (156). This categorization has been adopted by the reporting guidelines of the BSG from 2013 and by the ECCO guidelines of UC from 2012 and by several experts on IBD pathology (99), (138), (124), (133). Survey results revealed that pathologists rather tend to look at the crypts (95.6% of the respondents) than at the mucosal surface (61.2% of the respondents) to evaluate architectural abnormalities.

Villous surface has been showed to be a predictive feature of UC (157), (158). Surawicz et al. described villous surface as “resulting from a separation of the crypts and yielding a surface contour of broad villiform projections” (105). Selendrik et al. classified the severity of surface abnormalities in “irregular” with a villous crypt ratio between 1 and 1:5 and in “villous” with a villous crypt ratio of more than 1:5 (159). Schumacher et. al. defined villous mucosa as “wide crypt mounds giving the mucosal surface a villous or finger-like appearance” (106). The Second ECCO consensus paper of Diagnosis and Management of UC mentioned the definitions above (133). The phenomenon villiform change of the surface was seen very subjectively among the survey participants, since 34.2% agreed on the definitions mentioned in the guidelines, 32.0% did not and the remaining 33.7% did not know the definition of villiform change.

Assessment of pathological changes in crypt architecture is an important step in histologic IBD diagnosis as it reflects chronic inflammatory damage of the mucosa, (105), (107), (109), (120), (133) (160), (161). ECCO guidelines and expert groups (49), (99), (126), (133) define crypt distortion as an umbrella term for non-parallel crypts, variability in diameter or cystically dilated crypts. Crypt branching is described as a regenerative process through fission and is defined by the presence of at least two bifurcated crypts in a properly oriented biopsy specimen with a minimum of 2 mm of lamina muscularis mucosae (99) (107), (110). Rubio et. al. further divide branching into symmetric and asymmetric branching bearing a possible prognostic impact (162). Crypt branching can display various morphologies depending on the kind of specimen (biopsy vs. resection) and biopsy orientation and therefore still requires a consensus definition (110).

The second consensus guidelines from ECCO define crypt distortion as “irregularities in crypt size (i.e. variable diameter), spacing, orientation (i.e. loss of parallelism), or shape (including branching with a cystic configuration)” (133). Langner et. al., Villanacci et. al. and the European consensus of histopathology define crypt distortion as loss of their parallel arrangement, variability in crypt diameter or dilatation of the crypts. Crypt distortion and branching are, however, in some publications mentioned as distinct phenomena (49), (99), (110), (126). British reporting guidelines state that crypt distortion “may include branching, loss of parallelism, irregularity, tortuosity, dilatation and variation in shape and size”. The authors included crypt branching in the term “distortion” and wider spaced crypts in the term “atrophy” (138). The phenomenon of varying intercryptal distance is categorized under the term “crypt density” by the second consensus guidelines from ECCO, by Jenkins et.al., and Langner et.al., specifically, “as separation of adjacent crypts by lamina propria equivalent to or greater than one crypt diameter” (99), (107), (133). The majority (90.2%) of pathologists included crypt branching into the definition of distortion, as mentioned in thee ECCO consensus guidelines. However, study participants seemed to have varying opinions on other features of crypt distortion: More than half of the pathologists considered variability of internal diameter (56.8%) and intercryptal distance (65.6%) as features of distorted crypts. Thus, there remained a degree of subjective interpretation among the participants on the definition of crypt distortion but overall agreement over crypt branching being a feature of crypt distortion was strong.

Several authors and guidelines defined a cut-off of over 10% or two or more crypts being distorted in a well oriented sample with at least two mm length of lamina muscularis mucosae as a pathological finding (107), (117), (124), (126), (49), (163). In quantification of crypt distortion pathologists tended more likely to render the definitive diagnosis of crypt architectural distortion if more than two out of ten crypts display distorted architecture (in 57.7% of the cases). The cut-off of two out of ten was favored over less than two out of ten crypts being distorted (28.6% vs. 13.7%).

Jenkins et al. and Langner et. al. define crypt atrophy as crypt shortening; specifically, as “increased, usually variable, distance between the crypt bases and the muscularis mucosae” and “accompanied by an increased layer of lamina propria stroma between the crypt basis and the muscularis mucosae”, respectively. Decreased crypt density is described in both study groups as crypts being wider separated, specifically, by more than one crypt diameter (99), (107). Villanacci et. al also characterize atrophy by crypt shortening (49). Also, Washington et al., who have adopted the definitions above, mention both terms “atrophy” and “loss” separately in their study (111). On the other hand, the reporting guideline from the BSG and some other authors included wider distance between the crypts or thinned-out crypts also in the definition of crypt atrophy (106), (138), (157), (163). Furthermore, Cornaggia et al. define atrophy as decreased crypt number or crypt shortening or both (125). According to the ECCO Position Paper from 2020 crypt atrophy equals crypt shortening with increased space between the crypts as an “additional evidence” (135). The second and third ECCO consensus guidelines of UC describe crypt atrophy (shortened/thinned out crypts) with decreased density as distinct features which may occur in combination (109), (133). The majority of survey participants tended to consider both, crypt shortening and crypt loss as a definition of crypt atrophy in 72.5% and 69.8%, respectively.

Colitis is a term for inflammatory conditions of the colon with a wide range of etiologies (164), which can be divided into acute, chronic, and chronic active forms with each characteristic histological features depending on the pattern of injury. Irrespective of the predominant inflammatory pattern, chronic colitis displays inflammatory, architectural, or metaplastic features of chronicity. Active colitis often shows epithelial damage (165). Most of the survey participants tended to define “colitis” by the presence of both, inflammatory cells, and epithelial abnormalities rather than presence of inflammation alone (65.6% vs. 33.3%).

The majority of the participants (80.0%) required quite unanimously architectural abnormalities, mononuclear inflammatory infiltrate, and basal inflammatory cells for the definition of the term “chronic colitis”. Architectural distortion, chronic inflammatory infiltrates in the lamina, propria, metaplastic changes, and basal plasmacytosis are the represent hallmarks of chronic colitis (131), (165), which are clearly recognized by the survey participants.

Granulomas are of high diagnostic value for CD, but only if they are not associated to injured crypts, referred to as “cryptolytic granulomas” or related to foreign bodies (99), (107), (134), (166), (167). Cryptolytic granulomas frequently tend to occur in UC and other forms of colitis as well, often causing diagnostic difficulties (136), (168). The distinction between cryptolytic granulomas as an inflammatory response of crypt damage and non cryptolytic granulomas still remains a diagnostic challenge in differentiating CD from UC and shows a high interobserver variability (166). Granulomas along with histologic features of chronicity are diagnostically valuable towards CD and have high diagnostic sensitivity together with transmural lymphoid aggregates in the setting of fulminant IBD (97), (104). Their presence however is not obligatory for the diagnosis of CD (99), since they cannot always be identified: Granulomas have been found in biopsies and resection specimen in 13-50% and 40-60%, respectively (169). The survey results showed wide agreement (89.9%) among the participating pathologists that granulomas are a helpful diagnostic finding and are neither obligatory nor solely sufficient for diagnosis of suspected CD.

The terminal ileum is a frequent site of involvement in CD, sometimes also in an isolated form (87), (170), (171). Isolated ileitis lacking clinical symptoms or other inflammatory manifestations in the GIT without progression to CD in a long term follow up has already been described by Courvil et al. (172). Furthermore, NSAR, rheumatologic conditions, or infections may also cause inflammation in the terminal ileum (173). In the presence of a cecal patch or continuous inflammation in the caecum and the terminal ileum should arise cautious consideration not to confuse these findings with possible backwash ileitis of UC (99), (134). The majority of the participating pathologists (82.0%) shared the opinion that terminal ileitis is a helpful finding for the diagnosis of CD and is neither necessary nor sufficient on its own for confirming the diagnosis of CD.

Oberhuber et al. coined the term focally enhanced gastritis (FEG) and observed this kind of upper GI involvement in 76% of patients with CD (174). FEG is defined as a circumscribed inflammatory infiltrate composed of histiocytes, lymphocytes and neutrophils causing focal gastric gland destruction (175), (176). Parente et al. found FEG in 43% of CD and 12% of UC patients who were Helicobacter pylori negative (177). Sharif et. al. showed in their study a more frequent occurrence of FEG in CD compared to UC in a pediatric patient group (65.1% vs. 20.8%) (178). Roka et. al published similar findings in their retrospective study (176). ECCO consensus guidelines mention that the finding of FEG is possibly helpful in establishing the diagnosis of CD in difficult cases. However, despite being very common in IBD patients with a predominance in CD the differentiation between the two forms of IBD should not made solely based on this finding (126), (134), (179). There was much controversy among the survey participants concerning the diagnostic value of FEG in suspected IBD. Almost half of the pathologists (47.8%) replied that FEG is helpful for the diagnosis of CD reflecting the common knowledge among pathologists of FEG being more common in CD. According to 28.0% of the pathologists this finding is of diagnostic help for both UC ad CD and 22.0% did not see any value of FEG for IBD diagnosis.

Assessing alterations in inflammatory cell distribution is a main approach in diagnosing IBD (137). Distribution of lymphoplasmacytic infiltrate may be a helpful feature for differentiating IBD from microscopic colitis: In microscopic colitis inflammatory infiltrate is usually superficially accentuated, intraepithelial and, in contrast to IBD, mostly without basally located plasmacells and lymphoid aggregates. Also, in acute self-limiting colitis the predominantly neutrophilic infiltrate is rather more enhanced in the upper half of the mucosa. Assessment of distribution of inflammatory infiltrate can be useful for distinguishing IBD from diverticular colitis since the latter is located in areas with diverticula, predominantly in the sigmoid colon and spared the rectum (105), (161). Villanacci et al. showed that basal plasmacytosis present in multiple segments around the colon increases the likelihood for the diagnosis of IBD and found characteristic distribution patterns for both UC ad CD. The authors also observed a frequent presence of eosinophils among the basal plasmacells (108).

Evaluating the predominant composition of inflammatory cells together with other histologic findings may also be indicative of a certain type of colitis. Patil et Odze describe lymphoplasmacytic, (with or without neutrophils), predominantly neutrophilic, or eosinophilic, and paucicellular types of inflammatory patterns in the evaluation of colon biopsies. (161). When assessing inflammatory infiltrate in suspected IBD, its distribution was valued by the vast majority of participants (92.9%) as being the most helpful diagnostic feature to differentiate IBD from other forms of colitis. More than half of the pathologists (67.4%) considered the composition and 37.5% the density of the inflammatory cells as helpful in distinguishing other inflammatory differentials from IBD.

Since inflammatory cells of normal colonic mucosa are predominantly in the superficial third, increased lamina propria inflammatory infiltrate can be best assessed in the basal areas (107). Basal plasmacytosis is considered as an early finding and the strongest predictor for the diagnosis of IBD (14), (106), (108), (126). It is defined as plasma cells being located between the lamina muscularis mucosae and the basis of the crypts (99), (106), (108), (120), (163). European consensus on histopathology has adopted this definition (126). Some authors define basal plasmacytosis as occurrence of plasma cells at the base of the mucosa (168), or in the lower one third of the mucosa (103), The term “basal” (referring to basal plasmacytosis) is defined by the Second ECCO Consensus guidelines from 2012 as being present “around (deep 1/5th of the lamina propria) or below the crypts, alongside or penetrating the muscularis mucosae”. Basal can also mean being located in the basal part of the mucosa or between the crypt base and the lamina muscularis mucosae. The latter also refers to basally located lymphoid aggregates. (133). However, in order to apply the more exact definition, adequate orientation of the biopsy samples is mandatory to see the basis of the crypts otherwise they may be overlooked (151). When evaluating how pathologists defined “basal distribution” of inflammatory cells most of the participants favored the more precise definition: “Between the crypt base and the lamina muscularis mucosae” over “in the lower third of the lamina propria” (69.4% vs. 30.6%).

According to ECCO consensus guidelines, inflammatory infiltrate in IBD can be diffuse, focal, or patchy, according to its distribution in the lamina propria. Diffuse inflammation is defined as an “abnormal background cellularity with an overall increase in density [which] can either be superficial or transmucosal”. Authors state that lamina propria distribution can be assessed on one colonic level and use the term (dis)continuous in the sense of anatomic distribution of IBD. Furthermore, authors comment that using the term “discontinuous” as a synonym for “focal” and “patchy” may be misleading (124), (133). Langner et. al. describe the term “focal” as “increased cellularity of the lamina propria (with lymphocytes and plasma cells), of variable density throughout the biopsy specimen” (99). Guidelines of the BSG recommend using the terms “diffuse” and “focal” for describing distribution within a single site and not for topographic distribution of various levels in the GIT. In this case, authors prefer to use the terms “continuous between sites” or “discontinuous between sites/segmental” in the report (138). Tanaka et. al. defined the terms “focal” and “diffuse” to describe the corresponding histological changes in a single biopsy specimen or at the same level of the large bowel and favor the terms continuous and segmental to describe changes in different levels of the large bowel (163). Also, Lang-Schwarz et. al. prefer the use of the terms “continuous between sites”, “discontinuous/segmental between sites” to describe distribution of disease based on different biopsy sites over “focal or diffuse” which they consider to be subjective in this context (131). Cornaggia et. al. favor the same approach: Applying the terms “focal” or “diffuse” on biopsies from the same anatomical site and site and describing overall disease distribution either as continuous or segmental when anatomic tracts are spared (125). However, the terms “diffuse”, “continuous”, “focal” and “discontinuous” may often be used in subjective contexts (131). This tendency is mirrored in the survey results: The terms “diffuse(continuous)” and “discontinuous(focal)” for describing the distribution of inflammatory infiltrate were interpreted subjectively by the respondents. A greater percentage of pathologists defined “diffuse” as same density of inflammation in different biopsies from different sites rather than in one single biopsy (86.8% vs. 42.9%). For the term “discontinuous(focal)”, pathologists also favored the definition of variable density in different samples from different sites over variations in one biopsy (81.3% vs. 63.2%).

The terms “focal” and “patchy” are a matter of disagreement among participants since 53.2% made a distinction between the terms and the remaining 46.7% of the pathologists considered them as synonyms. Consensus guidelines from ECCO offer distinct definitions for both terms when describing distribution of inflammatory infiltrate: “Focal” is defined as ”normal background cellularity with areas of increased cellularity”, and “patchy” as “abnormal background cellularity with variable intensity” (133). British guidelines adopted this definition but state a lack of clear demarcation between the two terms (138). The third ECCO consensus document from 2017 doesn’t offer distinct definitions for the terms above (109). However “focal” or “patchy” imply variable density of inflammatory cells across the biopsy (99), (107). Study results reflect subjective interpretation for the terms “focal” and “patchy” among pathologists.

It is a well-known fact that UC usually affects the rectum and proceeds to more proximal areas of the colon. (14), (103), (180). According to Montreal classification, UC can manifest as ulcerative proctitis, left sided UC or extensive pancolitis beyond the splenic flexure and with varying disease extent over time (181). Left sided colitis has been frequently reported of some studies to be the predominant manifestation of UC (99), (180). The left colon as predominant location of UC has been clearly recognized by 92.9% of the pathologists.

In CD the right colon is according to the literature more likely to be affected (99), (126), often in combination with the terminal ileum (6). Most pathologists considered the right colon as the prevailing anatomic site involved in CD rather than equal affection of both colonic sites (69.4% vs. 27.9%).

Views concerning the diagnostic value of rectal sparing in suspected IBD varied among pathologists. The opinion that rectal sparing rules out UC was favored by 28.8% of the participants, although the literature mentions rectal sparing in biopsy studies in children with newly diagnosed UC (111), (182), in long standing disease or in course of local or systemic treatment (146), (147), (183), (184). Joo et Odze demonstrated on the other hand that none of the resection specimens of UC patients were completely devoid of rectal involvement (absolute rectal sparing) (185). The rectum is typically spared in CD (99), but association between rectal involvement and perianal lesions has been demonstrated (186).

Still, 8.7% considered rectal sparing as an exclusion criterion for CD. Half of the participating pathologists regarded rectal sparing having minor importance for the diagnosis of suspected IBD (50.5% of the cases). Some participants also did not regard rectal sparing as being helpful at all (12.0%) However, familiarity and awareness of rectal sparing seen in biopsy samples as potential atypical phenomenon in UC is important to avert rendering a wrong diagnosis especially changing the diagnosis from UC to CD (126), (127), (184).

Disease activity, depending on its severity, is characterized by the presence of neutrophil granulocytes and their damage to crypt, - and surface epithelium including cryptitis, crypt abscess, erosions and ulcerations (103), (125). Disease activity and extent of inflammation is rather measured clinically and endoscopically than upon histologic examination. However microscopic activity can be present in endoscopical quiescence (135). Since histologic activity has been shown to be a predictor for disease course, and therapy response (132), the pathologist should address disease activity in the final report according the ECCO consensus statement of UC (133). Despite lacking of standardized definition for histological healing (130), (132) pathologists should generally categorize UC in inactive, active or quiescent disease (99), (138). The vast majority of the pathologists (94.0%) usually defined disease activity in daily routine when dealing with UC as recommended in several guidelines and consensus documents (99), (109), (126), (131), (137).

Currently, literature in the field of activity in CD is sparse and clinicians seem to disagree on the relevance of activity for patient management (132), (134). Current ECCO consensus guidelines of CD do not recommend a specific system for grading active disease in CD (134). However, Pai et Geboes recommend microscopic evaluation of activity for each segment and in the most severely affected biopsy areas (132). Survey results showed that pathologists tended to grade disease activity in CD upon histology in 78.0% of the cases.

Most of the pathologists (79.8%) preferred a three tired system (e.g., mild, moderate, severe) over systems with two or more than three grades when assessing disease activity microscopically.

At least 26 scoring systems for CD have been proposed with Global Histologic Disease Activity score being most commonly used (132). Published scoring systems (like Geboes or Nancy index) for UC include grading of architectural changes, chronic inflammatory infiltrate, acute inflammatory infiltrate, erosions or ulcerations and crypt alterations by neutrophilic granulocytes (187), (188). Geboes score and Modified Riley Score count to the most commonly applied scoring systems for histologic disease activity in IBD (150), (189). Bressenot et al. found good reproducibility and interobserver agreement as well as good correlation among the latter (189). Nancy Index is shown to be user-friendly with full validation (135),(137). The expert panel from ECCO recommends a description of disease activity and/or use a formal activity score; for randomized control trials Nancy or Robarts histopathology index is recommended and Nancy Index for routine diagnostic workup (137), (135). A uniformly approved system for assessing activity is still lacking (190). This issue is reflected in the survey results since most of the participating pathologists (63.7%), did not apply a published scoring system like Nancy Index, Geboes Score or Riley Index in daily routine for assessment of histological activity. Merely 26.4% of the pathologists used an officially published index.

Neutrophilic granulocytes and their damage to the epithelium causing erosions and ulcerations play an essential role in disease activity (124), (131), (150), (191). There is broad overall consent among the participants about the features of activity: Pathologists widely agreed that the presence (81.8%) and localization (77.0%) of neutrophilic granulocytes and mucosal injuries like erosions and ulcerations (85.0%) are major hallmarks of active disease. Epithelial regeneration may be present in quiescent or active disease as a result of chronic inflammatory damage (49), (126). More survey participants regarded presence of other epithelial changes like regenerative/recovering epithelium as a minor feature of disease activity than as a major hallmark of active IBD (57.0% vs. 29.7%)

Both UC and CD harbor the risk of developing colorectal carcinoma (192) (193), (194), (195). Therefore, histologic diagnosis and categorization of dysplasia are crucial for subsequent patient care and risk stratification for colorectal cancer (120). Pathologists should include the presence and grade of dysplasia in the report and, due to high inter-observer variability, seek confirmation by an expert gastrointestinal pathologist (109), (126), (137). The importance of grading dysplasia was universally recognized among the pathologists. Nearly every survey participant graded dysplasia (98.9%).

Guidelines recommend the categorization of true dysplasia according to Riddell et. al. in two distinct grades: low and high-grade (122), (126), (196) which seemed to be widely adopted among pathologists (91.2%). A no longer recommended three tired grading scale (low, moderate, high grade) was carried out by very few participants (7.7%).

Colitis associated dysplasia occurs only in chronically inflamed areas and can be present as flat or elevated lesions (126). Sporadic adenomas and IBD-associated dysplasia seem to display different genetic alterations. IBD-associated dysplastic lesions are frequently associated with development or presence of carcinoma. However, a reliable distinction remains a matter of difficulty but if an adenoma is found in a non-colitic segment, it is probably a sporadic adenoma. (74). ECCO guidelines on histopathology summarize histological hallmarks and clinical features to differentiate colitis-associated dysplasia from Adenoma-like lesions (sporadic adenomas) and stress the importance of distinguishing the two entities due to different patient management. (126). Differentiation between sporadic adenoma and colitis-associated polypoid dysplastic lesions has been important due to substantial impact on patient treatment since for the latter colectomy has been formerly the recommended treatment. Adenomas not related to colitis-associated areas were treated by endoscopic polypectomy (197).

Guidelines from the Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International consensus recommendations (SCENIC) have recently proposed a different therapeutic approach: They propose a categorization into endoscopically visible (further categorized into polypoid or non-polypoid lesions) or invisible (detected only histologically on random biopsies) dysplastic lesions and recommend a complete endoscopic resection and continued surveillance for polypoid dysplasia in IBD over colectomy (198). Invisible high-grade dysplasia or a dysplastic lesion which is endoscopically not removable is an indication for colectomy. Colectomy or surveillance in cases of low grade flat dysplasia is still a matter of controversy (88). Study results showed that differentiation between colitis-associated, and colitis-independent (sporadic) dysplasia was widely recognized and performed commonly (in 78.1% of the cases) among survey participants.

Although regenerative changes in some cases may resemble dysplasia morphologically, nuclei from epithelial cells maturate towards the surface in contrast to dysplasia. In this case, maturation is missing or sparse and the dysplastic cells spread along the crypt axis to the surface (199). Surface maturation is characteristic for non-dysplastic regenerating cells (200). It is common knowledge among survey participants (in 98.0%) that surface maturation indicates regeneration and not dysplasia.

Dysplastic epithelium only present in the crypt epithelium does not exclude the definitive diagnosis of dysplasia according to the most respondents (70.3%). About one fourth of the pathologists (24.2%) would not report crypt restricted dysplastic epithelium (not reaching the surface) as dysplasia.

The tumor suppressor gene P53 is frequently mutated in early evolution of IBD-associated CRC in contrast to sporadic CRC in which case it has been found to be a genetic event occurring in later phases of carcinogenesis (201), (202), (203), (204). Many studies observed a positive p53 reaction upon immunohistochemistry in dysplastic lesions and colorectal carcinoma in the background of IBD (205) .P53 immunochemistry is considered to be a specific marker of dysplasia (203), but positive reaction may also occur in inflamed, reactive, regenerative or even normal mucosa (99), (126), (196) and therefore limits its diagnostic value. Although p53 immunohistochemistry is, however, considered to be helpful to differentiate UC-associated neoplasia from normal epithelium or inflammation related epithelial changes it is not recommended to be routinely used (99), (126), (196), (206), (207).

According to study results routine use of P53-immunohistochemistry did not seem to be a common practice among the responding pathologists. Almost half of the pathologists (49.2%) claimed to use p53-Immunostaining sometimes, 27.1% did never stain p53 in case of suspicious dysplastic lesions. Merely 11.6% always made use of p53-immunocheistry. The results reflect the diagnostic insecurity lying in the use of p53 in assessment of dysplasia in IBD.

Ki67-stain also is a marker for increased proliferation and is found to be expressed significantly higher in high-grade dysplasia in UC (208), (209). Some authors suggested that a positive Ki67 expression in the lower or basal third of the crypts excludes a lesion being dysplastic (203), (205). Several studies found an expansion beyond the basal third of the crypts of positive Ki-67 stain up to the superficial area in high-grade dysplastic crypts (203), (208), (210), (211), but also a higher expression in inflamed mucosa (209). Ki-67 staining seemd to be used even less frequently than p53-immunostaining: It has been sometimes applied by 46.2% and never by 38.5% of the participants. ECCO guidelines do not offer recommendations regarding Ki-67 immunochemistry for routine dysplasia assessment (109), (133), but however, Ki-67 seems to be an auxiliary marker in diagnosis of dysplasia (205).

Macroscopic workup of resection specimens

Taking photos of a resection specimens is not a consistent practice among pathologists since 55,9% of the respondents usually took photos in macroscopic workup of gross specimen with IBD, despite photographic documentation is recommended in current ECCO guidelines and from expert pathologists (99), (126), (137), (212).

Experts stress to carry out macroscopic workup in a structured and systematic fashion (49), (137). ECCO guidelines provide details on how to deal with resection specimens including sampling procedure and macroscopic workup (137). More than half of the pathologists (63.0%) replied that their institution provides strict instructions and criterions concerning tissue sampling of resection specimens.

Burroughs et. al. recommend taking samples every 10 cm between the two resection margins and also sampling focally visible lesions (212). Also, Sheffield et Talbot recommend a maximum spacing for sampling intervals of 10cm for evaluation of disease extent (213). Authors of the ECCO topical review recommend sequential sampling every 10 cm or less plus focal lesions “in diffuse visible disease and suspected dysplasia” (137). An ideal number of required tissue samples for a colectomy specimen has not been established so far (126). Overall sampling practice of regions with inflamed mucosa seemed to be quite accurate among pathologists. Half of the participants (50.8%) took sections every 10 cm in inflamed mucosa even if there is no suspicion for dysplasia or cancer. 40.3% even prefer biopsy intervals of 5 cm or closer. Only very few participants (7.1%) consider just one or two probes as sufficient for confirming diagnosis of IBD in the absence of suspicion for dysplasia.

Experts stress the necessity of taking samples from normal regions as well as from macroscopically visible lesions (99), (137). Most of the participating pathologists (88.3%) followed this recommendation and always sampled also normally looking mucosa apart from the two resection margins in resection specimens, 10.0% at least sometimes.

Inflamed mucosal areas remote from the tumor in resection specimens with IBD-associated carcinoma were always sampled by most of the participants (88.4%) to search for synchronous dysplasia. 11.1% occasionally sample mucosa remote to the tumor. There are no specific sampling recommendations on this issue in current literature so far, but it is known that in the presence of certain forms of dysplasia like flat high-grade dysplasia the risk of synchronous carcinoma is higher (99). Sheffield et. Talbot however, recommend to sample other mucosal lesions other than the tumor (213).

Summarized conclusions

Clinician's practice of biopsy handling tended to vary regarding the number of biopsies per site and number of submitted tissue containers, but the latter often being too sparse according to the standard sampling protocol. In general, however, separation of biopsy material, especially the rectum is performed by the clinicians. Guideline recommendations of sampling at least two biopsies per anatomic site was strictly followed by the clinicians. Ileal biopsies were sampled frequently, the upper GIT more often in pediatric patients than in adults. Provided patient related information was often insufficient, especially treatment history and symptom duration. Stricter guideline adherence is required to enhance diagnostic accuracy of the pathologists in this issue.

Laboratory handling showed variations regarding orientation and sectioning. Tissue orientation of biopsies is still not universally practiced. H&E staining and serial sections were preferred for routine diagnosis.

Study results showed partly divergent opinions on definitions of crypt distortion the terms "continuous" and "discontinuous" as well as "focal" and "patchy" in describing inflammatory infiltrate reflecting the subjectivity of these terms. Stricter consent has been showed on definitions of crypt atrophy, describing basally located inflammation and on the diagnostic value of granulomas and terminal ileitis in IBD diagnosis.

The diagnostic value of rectal sparing and focal enhanced gastritis showed different interpretations. Major features of chronicity and neutrophilic granulocytes and surface defects were uniformly recognized as major hallmarks of disease activity. Defining activity is common in UC as well as in CD but published grading systems, however, were not commonly applied. A three tired scoring system for assessing disease activity was preferred by most pathologists.

Grading of dysplasia is common practice preferably with a two-tiered system, as recommended in the guidelines. Distinction between colitis-associated and colitis-independent dysplasia was widely recognized. Use of Immunohistochemistry was individual, but not very frequently applied for lesions suspicious of dysplasia.

Macroscopical work-up of resection specimens, documentation and sampling showed some degree of variation among pathologists. Structured systematic rules or macroscopic recommendations were usually provided from the respective departments but this is not universal practice. Macroscopic sampling of the pathologists tended to be accurate but photographic documentation is performed inconsistently.

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