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Endoscopic tissue sampling – Part 2: Lower gastrointestinal tract. European Society of Gastrointestinal Endoscopy (ESGE) Guideline

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Table 1 s
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RECOMMENDATIONS

1 ESGE suggests performing segmental biopsies (at least two from each segment), which should be placed in different specimen containers (ileum, cecum, ascending, trans-

verse, descending, and sigmoid colon, and rectum) in patients with clinical and endoscopic signs of colitis.
Weak recommendation, low quality of evidence.

2 ESGE recommends taking two biopsies from the right hemicolon (ascending and transverse colon) and, in a separate container, two biopsies from the left hemicolon (descending and sigmoid colon) when microscopic colitis is suspected.
Strong recommendation, low quality of evidence.

3 ESGE recommends pancolonic dye-based chromoendoscopy or virtual chromoendoscopy with targeted biopsies of any visible lesions during surveillance endoscopy in patients with inflammatory bowel disease.
Strong recommendation, moderate quality of evidence.

4 ESGE suggests that, in high risk patients with a history of colonic neoplasia, tubular-appearing colon, strictures, ongoing therapy-refractory inflammation, or primary sclerosing cholangitis, chromoendoscopy with targeted biopsies can be combined with four-quadrant non-targeted biopsies every 10 cm along the colon.
Weak recommendation, low quality of evidence.

5 ESGE recommends that, if pouch surveillance for dysplasia is performed, visible abnormalities should be biopsied, with at least two biopsies systematically taken from each of the afferent ileal loop, the efferent blind loop, the pouch, and the anorectal cuff.
Strong recommendation, low quality of evidence.

6 ESGE recommends that, in patients with known ulcerative colitis and endoscopic signs of inflammation, at least two biopsies be obtained from the worst affected areas for the assessment of activity or the presence of cytomegalovirus; for those with no evident endoscopic signs of inflammation, advanced imaging technologies may be useful in identifying areas for targeted biopsies to assess histologic remission if this would have therapeutic consequences.
Strong recommendation, low quality of evidence.

7 ESGE suggests not biopsying endoscopically visible inflammation or normal-appearing mucosa to assess disease activity in known Crohn's disease.
Weak recommendation, low quality of evidence.

8 ESGE recommends that adequately assessed colorectal polyps that are judged to be premalignant should be fully excised rather than biopsied.
Strong recommendation, low quality of evidence.

9 ESGE recommends that, where endoscopically feasible, potentially malignant colorectal polyps should be excised en bloc rather than being biopsied. If the endoscopist cannot confidently perform en bloc excision at that time, careful representative images (rather than biopsies) should be taken of the potential focus of cancer, and the patient should be rescheduled or referred to an expert center.
Strong recommendation, low quality of evidence.

10 ESGE recommends that, in malignant lesions not amenable to endoscopic excision owing to deep invasion, six carefully targeted biopsies should be taken from the potential focus of cancer.
Strong recommendation, low quality of evidence.

SOURCE AND SCOPE

This Guideline is an official statement of the European Society of Gastrointestinal Endoscopy (ESGE). It provides guidance on the collection and handling of tissue samples during endoscopy of the lower gastrointestinal tract. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was adopted to define the strength of recommendations and the quality of evidence.

1 Introduction

Adequate collection and handling of tissue samples during endoscopy is fundamental in diagnosing pathology of the digestive system. The aim of this guideline was to make evidence-based recommendations on the indications and protocols for endoscopic tissue sampling for the most common conditions in the upper and lower gastrointestinal tracts and the hepatopancreatobiliary (HPB) tract. The upper gastrointestinal and HPB tracts were covered in Part 1, which was published separately [1].

Part 2 of this guideline will focus on the lower gastrointestinal tract. Colonoscopy is one of the most exploited endoscopic procedures for screening, diagnostic, and surveillance purposes. Despite the accuracy of endoscopy in detecting macroscopic lesions, several diseases require an optimized biopsy protocol. This guideline aims to provide evidence-based tissue sampling protocols for colonoscopy procedures performed in patients with clinical signs of colitis, known inflammatory bowel disease (IBD), including surveillance of pouch patients, and those with potential premalignant lesions or colorectal cancer.

ABBREVIATIONS

BLI	blue-light imaging
CRC	colorectal cancer
ESGE	European Society of Gastrointestinal Endoscopy
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HGD	high grade dysplasia
HPB	hepatopancreatobiliary
IBD	inflammatory bowel disease
LCI	linked color imaging
LGD	low grade dysplasia
MES	Mayo endoscopic score
NBI	narrow-band imaging
NHI	Nancy histological index
NSAID	nonsteroidal anti-inflammatory drug
OR	odds ratio
PICaSSO	Paddington International Virtual ChromoendoScopy ScOre
PICO	population, intervention, comparator, outcome
PSC	primary sclerosing cholangitis
RCT	randomized controlled trial
RHI	Robarts histopathology index
SES-CD	Simple Endoscopic Score for Crohn's disease
UC	ulcerative colitis
UCEIS	Ulcerative Colitis Endoscopic Index of Severity
WLE	white-light endoscopy

2 Methods

The European Society of Gastrointestinal Endoscopy (ESGE) commissioned this Guideline (Guideline Committee Chair, J. v. H.) and appointed a guideline leader (R.P.) who invited the listed authors to participate in the project development. After the project group had been assembled, task forces were formed to define the key questions and PICOs (population, intervention, comparator, outcome) in the upper gastrointestinal, lower gastrointestinal, and HPB domains (**Table 1 s**, see online-only Supplementary material). Literature searches and reviews of relevant articles were performed between March and September 2020. The available evidence was graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [2]. Based on the available evidence, recommendations and suggestions were drafted and discussed with the project group during online meetings. Further details on the methodology of ESGE guidelines have been reported elsewhere [3].

In July 2021, a draft prepared by the leaders and coordinating team was sent to all group members. The manuscript was also reviewed by two independent reviewers and sent for further comments to the ESGE National Societies and individual members. After agreement on a final version, the manuscript was submitted to the journal *Endoscopy* for publication. All authors agreed on the final revised manuscript. All recommendations in this guideline are summarized in ▶ **Table 1**.

This Guideline was issued in 2021 and will be considered for review and update in 2026, or sooner if new and relevant evidence becomes available. Any updates to the Guideline in the interim will be noted on the ESGE website: http://www.esge.com/esge-guidelines.html.

3 Colitis

3.1 Clinical and endoscopic signs of colitis

RECOMMENDATIONS

ESGE suggests performing segmental biopsies (at least two from each segment), which should be placed in different specimen containers (ileum, cecum, ascending, transverse, descending, and sigmoid colon, and rectum) in patients with clinical and endoscopic signs of colitis.
Weak recommendation, low quality of evidence.

ESGE suggests the pathologist should be informed of the endoscopic features of the colitis and any relevant clinical data.
Weak recommendation, low quality of evidence.

In patients with clinical and endoscopic signs of colitis without an already established diagnosis, it is recommended that at least two biopsies be obtained from seven segments (terminal ileum, cecum, ascending, transverse, descending, and sigmoid colon, and rectum), including if some segments are endoscopically normal. Biopsies should be placed into a separate container for each segment. This biopsy strategy increases the chance of a reliable diagnosis, including where there is a suspicion of Crohn's disease or ulcerative colitis (UC) [4, 5]. In a prospective consecutive cohort study, it was demonstrated that performing segmental biopsies and informing the pathologist about the endoscopic features and clinical data resulted in the etiology of the colitis being correctly identified in 100 % of cases. This study included patients with IBD, infections, graft-versus-host disease, microscopic colitis, nonsteroidal anti-inflammatory drug (NSAID) colonopathy, and amyloidosis [4].

Because the mucosal changes on histology may appear similar (e. g. in cases of infectious and ischemic colitis), clinical data are indispensable for the pathologist and an integral part of correctly diagnosing the etiology of the inflammation.

It is only where an endoscopic spot diagnosis (e. g. pseudomembranous colitis, ischemic colitis) can be made that segmental biopsies may not be necessary.

▶ **Table 1** Summarized recommendations for tissue sampling in the lower gastrointestinal tract.

Suspected diagnosis or indication	Number and location of biopsies	Remarks
Clinical and endoscopic signs of colitis	Segmental biopsies (at least two from each segment) placed in different specimen containers (ileum, cecum, ascending, transverse, descending, and sigmoid colon, and rectum)	Inform the pathologist of the endoscopic features of the colitis and relevant clinical data
Clinical suspicion but no endoscopic signs of colitis	Two biopsies from the left hemicolon (descending and sigmoid colon) and two from the right hemicolon (ascending colon and transverse colon)	Place biopsies from the left and right hemicolons into separate containers
Surveillance endoscopy in patients with known IBD	Pancolonic dye-based or virtual chromoendoscopy with targeted biopsies of any visible lesions In high risk patients (history of colonic neoplasia, tubular-appearing colon, strictures, ongoing therapy-refractory inflammation, PSC), chromoendoscopy with targeted biopsies can be combined with four-quadrant non-targeted biopsies every 10 cm along the colon	
Surveillance endoscopy in pouch patients	Biopsies of visible abnormalities and at least two biopsies from each of the afferent ileal loop, the efferent blind loop, the pouch, and the anorectal cuff	Place biopsies from different locations into separate containers
Evaluation of disease activity or remission in patients with known ulcerative colitis	For patients with endoscopic signs of inflammation, at least two biopsies from each segment, preferably from the worst affected areas, to assess disease activity or for CMV For patients with no evident endoscopic signs of inflammation, advanced imaging technologies may be useful in identifying areas for targeted biopsies to assess histologic remission if this would have therapeutic consequences	
Evaluation of disease activity in patients with known Crohn's disease	No biopsies of endoscopically visible inflammation or normal-appearing mucosa are recommended	
Potentially premalignant lesions	Adequately assessed colorectal polyps judged to be premalignant should be fully excised rather than biopsied	
Suspicion of colorectal cancer	Where endoscopically feasible, potentially malignant colorectal polyps should be excised en bloc rather than biopsied; if en bloc excision is not possible, careful representative images should be taken of the potential focus of cancer, and the patient should be rescheduled or referred to an expert center For malignant lesions that are not amenable to endoscopic excision owing to deep invasion, six carefully targeted biopsies should be taken from the potential focus of cancer	To reduce the risk of contamination and tumor seeding, forceps and snares used to sample or resect a potentially malignant lesion should not be reused; wherever possible, cancer sampling should be deferred until the end of the procedure

IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; CMV, cytomegalovirus.

3.2 Clinical suspicion but no endoscopic signs of colitis

RECOMMENDATION

ESGE recommends taking two biopsies from the right hemicolon (ascending and transverse colon) and, in a separate container, two biopsies from the left hemicolon (descending and sigmoid colon) when microscopic colitis is suspected.

Strong recommendation, low quality of evidence.

Where the scenario is that there is a clinical suspicion of colitis but with no clear endoscopic signs of colitis, microscopic colitis must be ruled out. The diagnosis of the different subtypes of microscopic colitis depends on the identification of certain microscopic changes in the colonic mucosal biopsies [6–8].

In collagenous colitis, the most typical feature on hematoxylin and eosin (H&E)-stained slides is an irregular thickening of the subepithelial collagen layer beneath the basement membrane: the normal thickness is 0–3 µm, whereas in collagenous colitis this increases to at least 10 µm, measured on well-oriented perpendicular sections. A Masson trichrome stain or an immunohistochemical stain for tenascin can be useful ancillary techniques to reach the diagnosis. An associated increased inflammatory cell infiltrate and possibly a detached surface epithelium can be seen. Importantly, the thickened subepithelial collagen layer may be unevenly distributed along the colon (being most prominent proximally, while it can be

entirely absent in the sigmoid colon and rectum in up to a third of cases) [7].

In lymphocytic colitis, the number of intraepithelial lymphocytes must be elevated above 20 per 100 surface epithelial cells (normal value <5 per 100). There is an associated increase in lamina propria inflammatory cells and possibly detachment of the surface epithelium, but no thickening of the subepithelial collagen layer. Lymphocytic colitis usually shows an even distribution throughout the colon, but the diagnostic findings may be patchy [7].

For the above-mentioned reasons, rectal biopsies alone appear insufficient for the exclusion of microscopic colitis and sampling within the range of flexible sigmoidoscopy may be inadequate. Therefore, a full ileocolonoscopy with biopsy sampling of the right hemicolon (one biopsy from the ascending colon and one biopsy from the transverse colon) and left hemicolon (one biopsy from the descending colon and one biopsy from the sigmoid colon) should be performed [11, 12]. The biopsies from the right and left hemicolon should be placed in separate containers and labelled as such [7–14].

4 Inflammatory bowel disease

4.1 Surveillance endoscopy in patients with known inflammatory bowel disease

RECOMMENDATIONS

ESGE recommends pancolonic dye-based chromoendoscopy or virtual chromoendoscopy with targeted biopsies of any visible lesions during surveillance endoscopy in patients with inflammatory bowel disease.
Strong recommendation, moderate quality of evidence.

ESGE suggests that, in high risk patients with a history of colonic neoplasia, tubular-appearing colon, strictures, ongoing therapy-refractory inflammation, or primary sclerosing cholangitis, chromoendoscopy with targeted biopsies can be combined with four-quadrant non-targeted biopsies every 10 cm along the colon.
Weak recommendation, low quality of evidence.

Current guidelines advise surveillance colonoscopy in patients with IBD be performed 8 years after the onset of the colitis (with the exception of those with proctitis or Crohn's colitis limited to one segment) for early detection of premalignant and malignant lesions [15]. Patients with longstanding UC and Crohn's colitis have an increased risk of developing colorectal cancer (CRC) when compared with the general population [16]. Disease extent, disease duration (CRC risk rises at a rate of 0.5 %–1 % per year after a disease duration of 8–10 years), degree of inflammation, presence of primary sclerosing cholangitis (PSC), and family history of CRC are all associated with an increased cancer risk [17, 18]. More recently, the presence of post-inflammatory polyps was found not to be independently associated with an increased risk of CRC [19]. Adequate bowel preparation, meticulous inspection, and high resolution equipment can optimize dysplasia detection [20, 21].

As compared with random biopsies on white-light endoscopy (WLE), the use of chromoendoscopy with targeted biopsies has increased the diagnostic yield for dysplasia [17, 22, 23]. A meta-analysis, including two randomized controlled trials (RCTs) showed a pooled incremental yield of chromoendoscopy over WLE for the detection of any grade of dysplasia on a per-patient basis of 7 % (95 %CI 3.2 %–11.3 %) with a number needed to treat of 14.3 [22]. More recently, a network meta-analysis of 27 studies showed that dye-based chromoendoscopy was associated with a higher likelihood of discovering dysplastic lesions than WLE [24]. A recent multicenter RCT showed no difference between the detection rate of colorectal neoplasia when patients were randomized to high definition WLE with random biopsy vs. high definition chromoendoscopy with targeted biopsy [25]. Additionally, in a randomized non-inferiority study, virtual chromoendoscopy or high definition WLE was not inferior to dye-based chromoendoscopy for the detection of colonic neoplastic lesions during surveillance colonoscopy [26]. A meta-analysis showed that, in RCTs, there was only a small benefit of dye-based chromoendoscopy over standard definition WLE, but no benefit over high definition WLE [27].

A prospective study examined 1000 patients undergoing surveillance colonoscopy for IBD. The standardized procedure was chromoendoscopy with targeted biopsies or endoscopic resection and then quadrant random biopsies taken every 10 cm [28]. An expert group of gastrointestinal pathologists agreed on the diagnosis of neoplasia, graded according to the Vienna classification as low grade dysplasia (LGD), high grade dysplasia (HGD), or cancer (indefinite for dysplasia was not considered neoplastic). A total of 140 neoplastic sites were found in 94 patients, 80 % of these from targeted biopsies or resections and 20 % from random biopsies. The yield of neoplasia from random biopsies was only 0.2 % per biopsy and 1.2 % per colonoscopy, but 12.8 % per patient with neoplasia. Importantly, dysplasia detected by random biopsies was associated with a personal history of neoplasia, a tubular-appearing colon, and the presence of PSC [28].

Another prospective multicenter RCT included 188 patients, of which 94 were randomized to high definition virtual chromoendoscopy and 94 to high definition WLE [29]. Targeted and quadrant non-targeted biopsies were taken in both arms. There was no significant difference in terms of neoplasia detection but, importantly, almost all neoplastic lesions were detected on targeted biopsy or resection, with quadrant non-targeted biopsies producing a negligible additional gain [29].

A recent retrospective cohort of 300 patients with colitis undergoing chromoendoscopy or high definition endoscopy for surveillance found that longer disease duration (odds ratio [OR] 1.04, 95 %CI 1.01–1.07), active inflammation (OR 2.89, 95 %CI 1.26–6.67), and concomitant PSC (OR 3.66, 95 %CI 1.21–11.08) were associated with the detection of dysplasia on random biopsies, compared with visible lesions [30].

There is no strong evidence to recommend biopsies from mucosa surrounding macroscopic lesions as the yield of these biopsies is low and does not change the management of the patient in comparison to the lesion itself [31]. In a retrospective study of 56 patients with IBD undergoing removal of dysplastic polyps, peripolyp biopsy specimens were assessed for dysplasia [32]. The diagnostic yield for dysplasia was 3.2 % and the presence of dysplasia was not associated with the risk of HGD or cancer during a median follow-up of 1.7 years. However, the grade of dysplasia of the polyp itself was predictive of subsequent advanced neoplasia. In line with this, in another retrospective study, dysplasia was detected in 5 % of biopsies collected from the surroundings of dysplastic lesions and post-resection surveillance did not reveal HGD or cancer [33]. Additionally, in a study of 131 patients undergoing 302 polyp resections or biopsies, dysplasia in adjacent biopsies was detected in only two patients (0.7 %) and was endoscopically visible in both cases [34].

4.2 Surveillance endoscopy in pouch patients

RECOMMENDATION

ESGE recommends that, if pouch surveillance for dysplasia is performed, visible abnormalities should be biopsied, with at least two biopsies systematically taken from each of the afferent ileal loop, the efferent blind loop, the pouch, and the anorectal cuff.
Strong recommendation, low quality of evidence.

Current guidelines suggest pouch surveillance in high risk patients [35, 36]. Epidemiologic data demonstrate an increased risk of pouch neoplasia over time ranging from 0.9 %–1 % after 5 years to 4.2 %–6.7 % after 20 years [37–39]. Based on the available data, pouch surveillance in high risk patients after colectomy for neoplasia seems reasonable 10–15 years after pouch construction. Available studies that have assessed the yield of biopsies demonstrate no clear beneficial effect of targeted or random biopsies for the identification of neoplasia in patients with a relatively short follow-up after pouch construction [40–45]. Most of these studies have however a relatively short follow-up of less than 10 years after pouch construction, while the epidemiologic data clearly indicate an increase in risk 15–20 years after pouch construction.

A prospective non-randomized trial assessed the sequential use of WLE and chromoendoscopy-targeted biopsies, followed by four random biopsies systematically taken from the afferent ileal loop, the efferent blind loop, the pouch, and the anorectal cuff [40]. One lesion with LGD was found with WLE. Chromoendoscopy revealed 14 suspicious lesions but none of them contained dysplasia. On the other hand, 672 random biopsies showed LGD in three biopsies (0.45 %). As the mean follow-up was only 8.6 years, it does not seem useful to perform biopsies early after pouch reconstruction. On the other hand, chromoendoscopy-targeted biopsies were insufficient to find the dysplasia that was present in these patients.

The additional need for random biopsies was illustrated in a retrospective study with 96 patients with pouch polyps and 998 without polyps (total of 1096 patients with 9 years of follow-up after pouch construction) [41]. In the polyp group, 3/96 patients had dysplasia (2 indefinite and 1 LGD), whereas 2/998 patients in the group without inflammatory polyps had neoplasia, but this was HGD and cancer found on non-targeted biopsies. Therefore, it seems insufficient to only target visible abnormalities.

Based on the available data, we recommend that, if one chooses to follow up pouch constructions in high risk patients with previous dysplasia, cancer, or PSC, at least after 10 years this should be by a combination of targeted and random biopsies, as data suggest that taking biopsies from visible abnormalities alone is insufficient.

4.3 Evaluation of disease activity or remission in patients with known ulcerative colitis

RECOMMENDATIONS

ESGE recommends that, in patients with known ulcerative colitis and endoscopic signs of inflammation, at least two biopsies be obtained from the worst affected areas for the assessment of activity or the presence of cytomegalovirus.
Strong recommendation, low quality of evidence.

ESGE recommends that, in patients with known ulcerative colitis and no evident endoscopic signs of inflammation, advanced imaging technologies may be useful in identifying areas for targeted biopsies to assess histologic remission if this would have therapeutic consequences.
Strong recommendation, low quality of evidence.

Endoscopy and histology are pivotal in assessing the activity of disease in UC. There is a growing body of evidence that histologic activity or histologic healing/remission may be an important therapeutic end point associated with improved patient outcome. In addition, histologic activity or chronic inflammation is likely to be an important risk factor for UC-associated neoplasia. Definitions for histologic remission of the mucosa include histologic normalization with absence of inflammation; absence of intraepithelial and lamina propria neutrophils/erosion/ulceration. Several studies and a meta-analysis have shown that 18 %–24 % of UC patients with endoscopic remission still have histologic changes and inflammation [46]. It is therefore suggested that assessment of histologic activity provides clinically important prognostic information, beyond that of endoscopic remission or clinical remission [46].

Several studies have aimed to correlate endoscopic activity with histologic activity and generally the relationship has been modest at best. However, these studies have been heterogeneous as most of them were single-center retrospective or prospective observational studies. This has resulted in variance of concordance between endoscopic activity and histologic activity. The likely reason for this disparity is that these studies have

used variable and nonvalidated endoscopic or histologic indices for the comparison [47–50]. Many histologic indices have been developed in the past decades to assess activity of the disease in UC, but only two have been fully validated and tested for responsiveness, namely the Nancy histological index (NHI) [51] and the Robarts histopathology index (RHI) [52]. Scores to endoscopically assess disease activity include the Mayo Endoscopic Score (MES), which is partially validated and is widely used by gastroenterologists for its simplicity [53], and the Ulcerative Colitis Endoscopic Index of Severity [UCEIS], which was validated in three independent cohorts and is mainly used in clinical trials [54].

In a single-center prospective observational study, the overall correlation between the validated UCEIS and RHI was numerically greater [$r = 0.86$, 95 %CI 0.80–0.90; $P < 0.001$] than between the UCEIS and NHI [$r = 0.84$, 95 %CI 0.76–0.89; $P < 0.001$] [55]. In contrast, in a recent multicenter international prospective study, the correlations between the endoscopic scores and Riley histologic score in quiescent UC were low [56]. Recently a large multicenter international "real life" study demonstrated that the MES, UCEIS, and the newly validated virtual chromoendoscopy score PICaSSO (Paddington International Virtual ChromoendoScopy ScOre) [57] correlated strongly with several histologic scores. Correlation of the PICaSSO with all histology scores was statistically superior to both the MES and UCEIS [57].

In view of the current data, biopsies are still recommended with a minimum of two biopsies from either the worst affected or the most representative area of mucosal healing, preferably at the edge of any ulcers. Histologic assessment of biopsies can be used to assess disease activity, the presence of cytomegalovirus, and histologic healing, to optimize therapy by either escalation or exit strategies, to predict long-term adverse outcome, and to manage patients to achieve their treatment target.

The endoscopic differences between quiescent, mild, and patchy activity of the disease are often difficult to detect, especially when using standard WLE. New advanced high definition endoscopic technologies and optical diagnosis and enhancement techniques, such as narrow-band imaging (NBI; Olympus Japan), iSCAN (iSCAN-OE; Pentax, Japan), linked color imaging (LCI; Fujifilm), blue-light imaging (BLI; Fujifilm, Japan), confocal laser endomicroscopy (CLE; Mauna Kea, France), and endocytoscopy (Olympus, Japan) can provide a better definition of the mucosal and vascular architecture (▶ **Fig. 1** and ▶ **Fig. 2**). In addition, artificial intelligence (AI) may play an important role in assessing histologic remission, but its use should first be prospectively validated. Although advanced imaging techniques cannot yet replace real histology, these techniques may be useful in identifying areas for targeted biopsies.

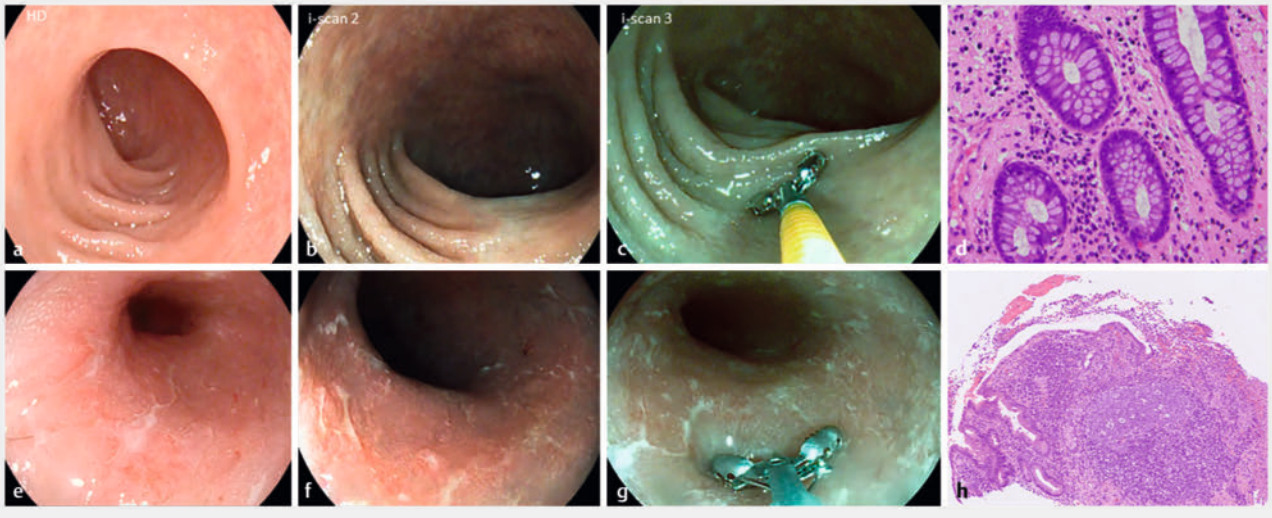
4.4 Evaluation of disease activity in patients with known Crohn's disease

RECOMMENDATION

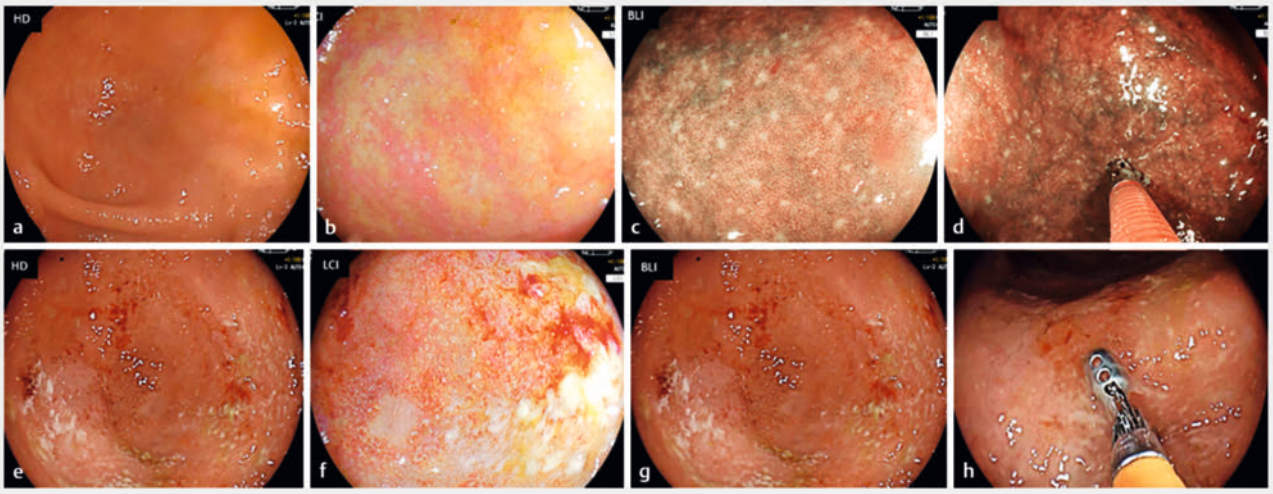
ESGE suggests not biopsying endoscopically visible inflammation or normal-appearing mucosa to assess disease activity in known Crohn's disease.

Weak recommendation, low quality of evidence.

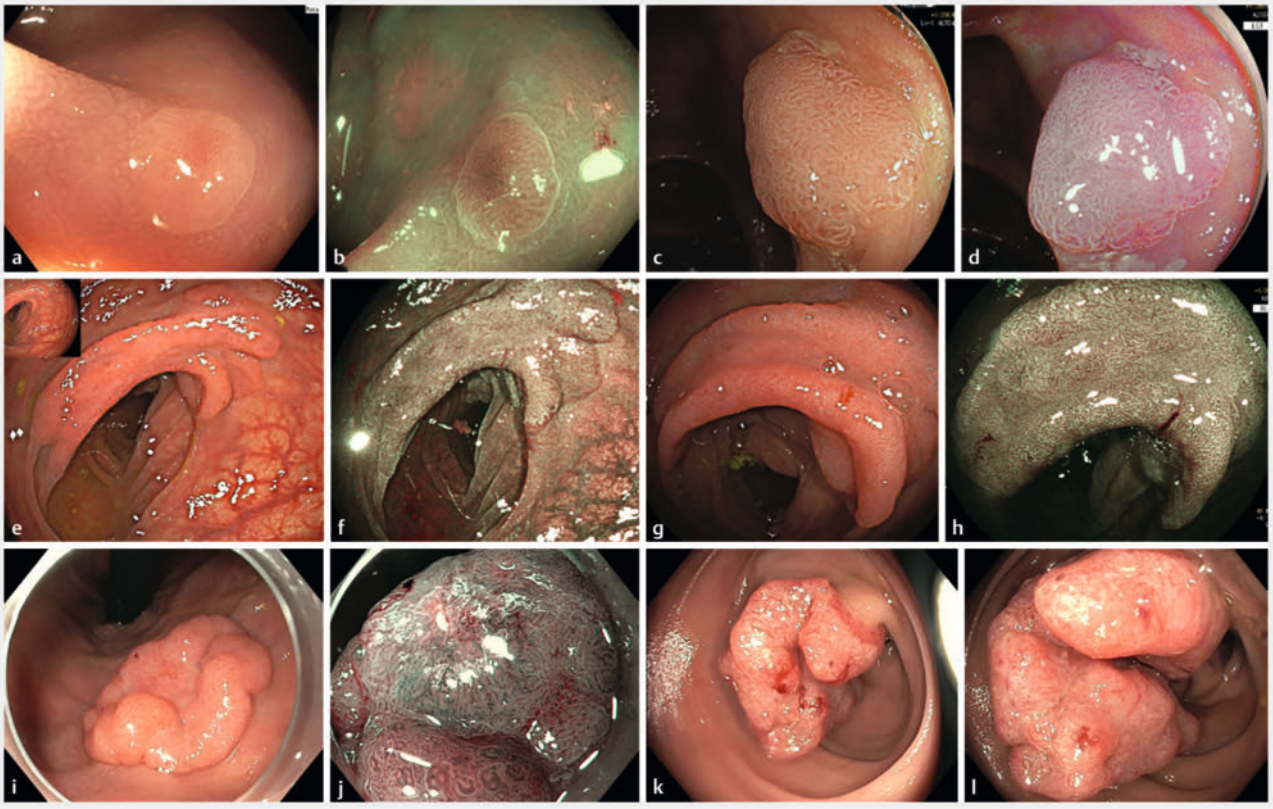
A recent systematic review summarized all the histologic scores that are used to score Crohn's disease activity histologically. This included 14 studies mentioning 13 different scores. The most commonly used score is the Global Histological Activity Score (GHAS), which has been modified in six other scores. The main problem is that none of these scores have been prospectively validated against endoscopic activity alone. Some scores are validated against clinical disease activity only [58].



▶ **Fig. 1** Use of advanced imaging techniques in ulcerative colitis. **a–c** Endoscopic appearance in quiescent ulcerative colitis imaged by: **a** white-light endoscopy (WLE); **b** i-scan 2 mode; **c** i-scan 3 mode; with **d** histological appearance on biopsy. **e–g** Endoscopic appearance in severe ulcerative colitis imaged by: **e** WLE; **f** i-scan 2 mode; **g** i-scan 3 mode; with **h** histological appearance on biopsy.



▶ **Fig. 2** Use of advanced imaging techniques in ulcerative colitis. **a–d** Endoscopic images demonstrating mild activity of ulcerative colitis imaged by: **a** high definition white-light endoscopy (WLE); **b** linked color imaging (LCI); **c** blue-light imaging (BLI); **d** BLI, which is used to guide biopsy sampling. **e–h** Endoscopic images showing moderate activity of ulcerative colitis imaged by: **e** high definition WLE; **f** LCI; **g** BLI; **h** BLI, with a biopsy being obtained from the worst affected area.



▶ **Fig. 3** Endoscopic images of potentially premalignant lesions in the colon and colorectal cancer showing: **a, b** a non-advanced tubular adenoma with low grade dysplasia (LGD) on: **a** near-focus high definition white-light endoscopy (WLE); **b** narrow-band imaging (NBI); **c, d** a non-advanced tubulovillous adenoma with LGD on: **c** high definition WLE; **d** linked color imaging; **e–h** an advanced lesion of > 10 mm that is carefully assessed, after washing, and found to have no foci suspicious of invasive malignancy (with final histology showing a tubular adenoma with LGD) on: **e, g** high definition WLE; **f, h** blue-light imaging; **i, j** an advanced lesion appearing atypical and suspicious for neoplasia on: **i** high definition WLE; **j** near-focus NBI where there is a suspicion of deep invasion based on the vascular and mucosal pattern (NICE type 3, JNET type 3); **k, l** advanced colorectal cancer, T2N1. Source: Dr. M. van der Vlugt and Dr. B.A.J. Bastiaansen.

The studies that are available have assessed, usually in retrospect, the correlation between endoscopic activity and histology [59–67]. The Simple Endoscopic Score for Crohn's disease (SES-CD) is the most commonly used endoscopic score. The correlations between histologic inflammation and SES-CD have ranged from very poor ($r = 0.182$) to good ($r > 0.79$). One interesting study assessed the importance of the location, in relation to the ulcer, from which the biopsy was taken. Interestingly, a significant decrease in histologic disease activity could be found with increasing distance from the edge of the ulcer. Even in close proximity, namely 7–8 mm from the edge, histologic inflammation was decreased. In addition, only a poor concordance in terms of remission was found between the histologic scores and the SES-CD [59].

In view of the lack of sufficient validation of histologic scores, variable correlation with endoscopic disease activity, and variability of biopsies even in close proximity to an ulcer, it seems that additional biopsies to assess histologic disease activity contribute very little to the clinical management of patients with a confirmed diagnosis of Crohn's disease. In addition, one may wonder if a mucosal biopsy is representative of a transmural disease. Because Crohn's disease has a patchy distribution, it is also possible that access to the most inflamed areas will be compromised by the presence of strictures. In this case, random biopsies of a less inflamed area accessed by colonoscopy or enteroscopy will not reflect the actual state of inflammation of the patient.

5 Potentially premalignant lesions and colorectal cancer

5.1 Potentially premalignant lesions

RECOMMENDATION

ESGE recommends that adequately assessed colorectal polyps that are judged to be premalignant should be fully excised rather than biopsied.

Strong recommendation, low quality of evidence.

5.1.1 Non-advanced lesions

In general, colorectal polyps should be fully excised rather than biopsied. This approach allows definitive histopathologic evaluation and should also be curative. However, some diminutive (≤ 5 mm) polyps, specifically rectal hyperplastic polyps, carry no malignant potential and, therefore, provided optical assessment is consistent with this diagnosis, these polyps need neither removal nor tissue sampling; where doubt remains, they should be fully excised (▶ **Fig. 3**) [68].

Whilst most other diminutive polyps are premalignant and should therefore be resected, endoscopic assessment of surface features (morphology, pit pattern, and vascular pattern) may accurately predict histology when performed by appropriately trained endoscopists, removing the need for histologic assessment of the resected specimen: ESGE suggests that virtual chromoendoscopy and dye-based chromoendoscopy can be used, under strictly controlled conditions, for real-time optical diagnosis of diminutive colorectal polyps and can replace histopathologic diagnosis [69]. ESGE also suggests the possible incorporation of computer-aided characterization of lesions during colonoscopy, if acceptable and reproducible accuracy for colorectal neoplasia is demonstrated in high quality multicenter in vivo clinical studies [69].

5.1.2 Advanced lesions

Large (> 10 mm) or atypical colorectal lesions (JNET type 2B or type 3 [70]; NICE classification type 3 [71]) require careful endoscopic assessment, with adequate washing and thorough inspection of the entire lesion, to identify potential foci of invasive malignancy (▶ **Fig. 3**). This is aided by the use of high definition endoscopes, in combination with (virtual) chromoendoscopy [69, 72]. Biopsies are not required if the endoscopist has thoroughly interrogated the lesion and has not identified any atypical features. This information can be supplemented with photographs or a video, which are usually more meaningful than isolated biopsies.

5.2 Suspicion of colorectal cancer

RECOMMENDATIONS

ESGE recommends that, where endoscopically feasible, potentially malignant colorectal polyps should be excised en bloc rather than being biopsied. If the endoscopist cannot confidently perform en bloc excision at that time, careful representative images (rather than biopsies) should be taken of the potential focus of cancer, and the patient should be rescheduled or referred to an expert center.

Strong recommendation, low quality of evidence.

ESGE recommends that, in malignant lesions not amenable to endoscopic excision owing to deep invasion, six carefully targeted biopsies should be taken from the potential focus of cancer.

Strong recommendation, low quality of evidence.

ESGE recommends that, to reduce the risk of contamination and tumor seeding, forceps and snares used to sample or resect a potentially malignant lesion should not be reused during that procedure and, wherever possible, cancer sampling should be deferred until the end of procedure.

Strong recommendation, low quality of evidence.

5.2.1 Biopsy tethering

If a lesion may be amenable to endoscopic removal, biopsies should be used with caution as there is a risk of submucosal tethering due to fibrosis, rendering the lesion unresectable [72]. The risk of tethering is highest when biopsies are taken from flat lesions or at the periphery of a lesion, and is even higher if a snare is used to partially resect or sample a lesion [68, 73]. Of interest, one study found that tethering only occurred 3 weeks

after biopsy [74]. Therefore, if the endoscopist cannot confidently perform en bloc excision during endoscopy (e.g. because of lack of experience, lack of patient consent, or use of anticoagulant therapy), careful representative images (rather than biopsies) should be taken of the potential focus of cancer, and the patient should be rescheduled or referred to an expert center.

5.2.2 Underdiagnosis

Biopsy sampling of advanced colorectal lesions carries the risk of missing the malignant focus within a polyp as only a small portion of the lesion is sampled. Studies of biopsy sampling of malignant colorectal polyps have reported false negative rates of 18.5%–86% [75–78]. Therefore, where the endoscopist is adequately experienced and confident that they can remove a suspicious lesion en bloc, this is usually the best strategy as it permits histologic assessment of the entire lesion, thereby minimizing the risk of underdiagnosis [78]. However, for highly suspicious lesions or where en bloc resection is not possible, biopsy sampling may be required (▶ **Fig. 3**). In this case, after careful inspection of the entire lesion, biopsies should be targeted to the area exhibiting features indicative of cancer, rather than taking non-targeted (random) biopsies of the lesion [72].

5.2.3 High grade dysplasia on biopsy

Particular caution should be given to the interpretation of HGD on a superficial biopsy of a lesion (as opposed to HGD seen in a fully histologically assessed polypectomy specimen), as there is an increased risk of malignancy within the lesion; the lesion should be assumed to be malignant until proven otherwise [79].

5.2.4 Number of biopsies

Several studies have assessed the optimal number of biopsy specimens to reduce the cancer miss rate. One study of 60 cancers found that the first four biopsies identified 41 cancers, whilst taking six biopsies identified 47 cancers [80]. No additional cancers were identified by taking further biopsies (up to 10 in total), but adding in cytology detected an additional eight cancers; five cancers remained undiagnosed despite biopsies and cytology. The authors concluded that the combination of cytology and four to six biopsies was recommended. Another study of 32 patients with advanced colon cancer revealed that the positive diagnosis rates for the first, second, and third biopsies were 78.1%, 87.5%, and 93.8% [81]. Further biopsies did not increase positive diagnosis cumulative rates, leading to the recommendation that three or four biopsies should be taken.

Reinforcing the need for careful assessment and targeted biopsies, a study demonstrated that the implementation of a quality improvement program increased the CRC yield of histologic sampling from 61% to 92% [82].

5.2.5 Contamination and tumor seeding

Another consideration regarding the biopsying of malignant lesions is the small risk of "carry-over" between specimens if a cancer is biopsied before a benign polyp, causing diagnostic confusion [68]. Furthermore, a recent study demonstrated that the colonoscope working channel became contaminated with viable tumor cells during biopsy collection and that subsequent instruments introduced through the channel became contaminated with cells that were shown to maintain their proliferative potential [83]. They also identified an identical molecular signature in primary and metachronous colorectal tumors where the most likely etiology was tumor seeding, concluding that, although the possibility of iatrogenic seeding seemed low, it was a potentially preventable cause of metachronous CRC, which could be reduced by simple adaptations, such as changing the order of procedures (e.g. tattooing the site before sampling the cancer).

Disclaimer

The legal disclaimer for ESGE guidelines [84] applies to this Guideline.

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Competing interests

M. Barret has received consultancy fees from Medtronic (2018 to present) and Pentax (2019 to present). R. Bisschops has received consultancy and speaker's fees from Fujifilm, Pentax, Medtronic (all 2015 to present), and Norgine (2016 to present), consultancy fees from Boston Scientific, Cook (both 2015 to present), CDx Diagnostics (2017 to present), and GI Supply (2018 to present), and speaker's fees from Medivators (2017 to 2018) and Ipsen (2020 to present); his department has received research grants from Fujifilm, Pentax (both 2015 to present), Cook (2016 to 2019), and Medtronic (2018 to present). M. Dinis Ribeiro is co-editor-in-chief of Endoscopy; his department has received a research grant from Fujifilm (2020 to present) and an educational grant from Olympus (2020 to present). M. Iacucci has received research grant support from Pentax (2016 to present), Olympus (2018 to 2020), and Fujifilm (2019 to present). M.C.W. Spaander has received research support from Boston Scientific (2013 to present) and Cook Medical (2009 to 2013). J.E. van Hooft has received lecture fees from Medtronic (2014, 2015, and 2019) and Cook Medical (2019), and consultancy fees from Boston Scientific (2014 to 2017) and Olympus (2021); her department has received research grants from Abbot (2014 to 2017) and Cook Medical (2014 to 2019). K. Biermann, L. Czakó, K.B. Gecse, G. de Hertogh, T. Hucl, M. Jansen, R.E. Pouw, M. Rutter, E. Savarino, P.T. Schmidt, and M. Vieth declare that they have no conflict of interest.

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Supplementary material

Endoscopic tissue sampling – Part 2: Lower gastrointestinal tract. European Society of Gastrointestinal Endoscopy (ESGE) Guideline

Roos E. Pouw, Raf Bisschops, Krisztina B. Gecse et al.

Table 1s – Overview of key questions.

Lower gastrointestinal (GI) taskforce:
1. What biopsy protocol should be used in case of clinical and endoscopic signs of colitis?
2. What biopsy protocol should be used in case of a clinical suspicion, but no endoscopic signs of colitis?
3. What biopsy protocol should be used during surveillance colonoscopy in patients with known inflammatory bowel disease?
4. What biopsy protocol should be used in pouch patients undergoing surveillance endoscopy?
5. Should biopsies be obtained in patients with known ulcerative colitis to evaluate disease activity or remission? And if so, which biopsy protocol should be used?
6. Should biopsies be obtained in patients with known Crohn's disease to evaluate disease activity?
7. What is the role of tissue sampling for potentially premalignant lesions in the colon?
8. What is the role of tissue sampling in case of a suspicion of colorectal cancer?

