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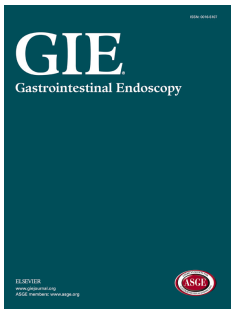


# Endoscopic management of patients with high-risk colorectal colitis-associated neoplasia: a Delphi study

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**Endoscopic management of patients with high-risk colorectal colitis-associated neoplasia: a Delphi study**

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**Abstract**

**Background and Aim**

Current guidelines recommend endoscopic resection of visible and endoscopically resectable colorectal colitis-associated neoplasia (CAN) in patients with inflammatory bowel disease (IBD). However, patients with high risk CAN are often not amenable to conventional resections techniques and a consensus approach for the endoscopic management of these lesions is presently lacking. This Delphi study aims to reach consensus amongst experts on the endoscopic management of these lesions.

**Methods**

A three-round modified Delphi process was conducted to reach consensus amongst worldwide IBD and/or endoscopy experts (n=18) from three continents. Consensus was considered if ≥ 75% agreed or disagreed. Quality of evidence was assessed by the criteria of the Cochrane Collaboration group.

**Results**

Consensus was reached on all statements (n=14). Experts agreed on a definition for CAN and high-risk CAN (HR-CAN). Consensus was reached on the examination of the colon with enhanced endoscopic imaging prior to resection, the endoscopic resectability of a HR-CAN lesion and endoscopic assessment and standard report of CAN lesions. In addition, experts agreed on type of resections of HR-CAN (< 20mm, >20 mm, with or without good lifting), endoscopic success (technical success and outcomes), histologic assessment and follow-up in HR-CAN.

**Conclusion**

This is the first step in developing international consensus-based recommendations for endoscopic management of (HR-)CAN. Although the quality of available evidence was considered low, consensus was reached on several aspects of the management of (HR-)CAN. The present work and proposed standardization might benefit future studies.

## Introduction

American and European guidelines recommend endoscopic resection for visible and endoscopically resectable colorectal dysplasia in patients with inflammatory bowel disease (IBD).(1-3) Two meta-analyses provide support for this strategy, but emphasize the need for close endoscopic follow-up due to the risk of recurrence (2 to 5.3/1000 person years of follow-up) and metachronous dysplasia.(4, 5)

Endoscopic resection of colitis-associated neoplasia (CAN), especially of larger lesions, can be challenging due to ongoing inflammation, mucosal scarring and submucosal fibrosis.(6) Both endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are used for the resection of CAN. These techniques are reportedly effective, safe in case of sporadic adenomas and are associated with low proctocolectomy rates for neoplasia.(7, 8) However, the optimal use of these techniques and the follow-up strategy in CAN is presently unclear.

Several studies have suggested that EMR and ESD are safe and feasible in the setting of CAN. (9-23) These relatively small, retrospective studies comprise a total of 552 patients (589 lesions).(9-23) Most patients were diagnosed with ulcerative colitis (UC).(9-23) Ten studies exclusively reported on ESD procedures.(9, 12, 14-17, 19-22) The remaining five studies described both ESD and EMR procedures (10, 11, 13, 18, 23) or ESD-assisted EMR.(10, 11, 13, 18, 23) A recent analysis of pooled data suggested *en bloc* and R0 resection rates of 86% and 70% for non-polypoid lesions with a potential superiority for ESD.(24) Following endoscopic resection, patients with non-polypoid dysplasia seem to have higher colorectal cancer (CRC) and metachronous neoplasia incidence rates, warranting closer endoscopic follow-up.(24) Of note, high-quality data from large prospective studies are lacking.

Current recommendations in guidelines are largely based on expert opinion, and important questions concerning the endoscopic management of CAN remain unanswered.(1-3) This study aims to generate a consensus on standardized endoscopic management of CAN, based on current evidence and expert opinion.

## Methods

*Development of consensus statements and literature review*

A modified Delphi approach was used to reach consensus on statements concerning the endoscopic management of CAN.(25) Members of the expert panel were invited by the senior authors (LM and BO) and had extensive IBD expertise (n=9) and/or were EMR/ESD experts (n=12). Prior to the first meeting in March 2021, a literature review was conducted by the study coordinator (MB) and one senior author (LM) in Medline

and EMBASE for relevant literature. PICOs were developed for several statements. Search strings of the PICOs are presented in **Supplementary File 1**. This literature search and the results were shared with all the invited experts. In the first phase, the literature was shared among all experts and the statements were drafted (**Figure 1**). In total, three online meetings were organized to discuss and reach consensus on the proposed statements. Following the meetings, participants were asked to vote electronically and provide feedback on the statements. In case of adjusted or new statements, the systematic review was updated. Feedback was incorporated into the second and third round of voting.

*Electronic voting rounds*

Experts were asked to vote on statements on a five-point Likert scale in three rounds of electronic voting ranging from 'strongly disagree' to 'strongly agree'. In the second and third round of voting, experts were given the overall results of each question of the prior voting round and their own voting. Only the study coordinator (MB) had access to the voting results. The senior authors were blinded to the feedback of the individual participants.

*Acceptance of statements and quality of evidence*

Consensus was defined as ≥ 75% agreement ('agree'/'strongly agree' or 'disagree'/'strongly disagree') on an individual statement.

Participants were asked individually to assess the quality of evidence of the provided literature. Quality of evidence was assessed with the criteria of the Cochrane Collaboration Review Group.(26) The final recommendation for the quality of evidence was based on the majority of the votes.

**Results**

*Participants*

In total, 18 experts from ten countries and three continents were invited to participate. Response rates in the first, second and third round of voting were 94.4% (n=17), 66.7% (n=12) and 94.4%(n=17), respectively. Quality of evidence was assessed by 83.3% (n=15) of the respondents.

*Consensus statements*

Results of the statements that reached consensus, in the third and final round of voting, are displayed in **Table 1**. Consensus was reached on all statements (n=14). Based on the statements, a flowchart was developed (**Figure 2**).Details on the third and final round of voting are presented in **Supplementary File 2**.

*Nomenclature of (high-risk) colitis-associated neoplasia*

***Statement 1: We suggest to adopt the term Colitis Associated Neoplasia (CAN) for all neoplastic lesions, detected in a section of previously or presently inflamed colon.***

***(Agreement: 100%, quality of evidence: no evidence)***

Patients with IBD have an increased risk of developing CRC.(27) Although most mechanisms underlying tumorigenesis in CAN are similar to those involved in sporadic CRC, timing and frequency of driver events differ.(28) Also, endoscopic features and clinical behavior of CAN diverge from sporadic adenomas or CRC. To date, no clear definition of CAN is provided in current literature and guidelines.(1-3) CAN develops in areas with chronic inflammation and may present as endoscopically visible or invisible lesions (the latter referring to lesions, identified by random biopsies). Visible lesions can be classified morphologically into polypoid and non-polypoid types.(29) Both colitis-associated adenomas and colitis-associated serrated lesions have been found to carry an increased risk of metachronous and synchronous multifocal visible dysplasia.(30)

Neoplastic lesions that are encountered in (previously) non-inflamed areas of the colon are considered to be sporadic adenomas, unrelated to colitis.(31) Results from previous studies do not indicate an increased risk of CRC development following endoscopic removal of these lesions(32-36), even when the resected polyps contain high-grade dysplasia (HGD).(37)

***Statement 2: Extent of previous or present inflammation should be/should have been confirmed by endoscopy and/or histology.***

***(Agreement: 100%, quality of evidence: no evidence)***

Confirmation of inflammation is warranted as CAN arises characteristically in previously or presently inflamed mucosa. Biopsies can be used to discriminate between quiescent disease and different grades of disease activity.(29, 38) According to the current European guidelines, biopsies should be accompanied by clinical information such as endoscopic findings.(29, 38) An adequate number of biopsies should be obtained from inflamed as well as non-inflamed mucosa as mild or even severe inflammation can be detected in endoscopically normal appearing mucosa.(29) Histologic disease activity in UC can be assessed with use of validated histological score indices (i.e., Geboes score, Nancy Index and Robarts Histopathology Index).(39)

To date, there is no validated histological scoring index for evaluation of Crohn's disease (CD) activity.(40) Several endoscopic scores have been established and used in clinical practice to monitor endoscopic activity for UC and CD. The most obvious candidates for UC are the formally validated the ulcerative colitis endoscopic index of severity (UCEIS) and the ulcerative colitis colonoscopic index of severity (UCCIS), while in CD the Crohn's disease endoscopic index of severity (CDEIS) or the simple endoscopic score for Crohn's disease (SES-CD) can be used.(41-44) The latter scores were shown to be highly reproducible with demonstration of excellent inter-observer agreement, and have been prospectively validated.(3)

***Statement 3: Non-polypoid lesions and large (>20 mm) non-pedunculated colon polyps (LNPCP) should be considered high-risk colitis-associated neoplasia (HR-CAN)***

***(Agreement: 88.2%, quality of evidence: limited evidence)***

Given its potentially worse outcome, an agreed-upon definition of high-risk colitis-associated neoplasia (HR-CAN) is desirable as it constitutes the first step towards a coherent therapeutic strategy. Two recent studies have identified non-polypoid lesions as an independent risk factor for (advanced) colorectal neoplasia development in patients with IBD.(45, 46) In addition, pooled data reported higher CRC and metachronous neoplasia incidence rates following endoscopic resection of non-polypoid lesions as compared to polypoid lesions.(5) In contrast, several studies have shown that polypoid lesions with low-grade dysplasia (LGD) or HGD in IBD patients have a low risk of future CRC.(35-37, 46, 47) Moreover, previous studies have shown that the risk of CRC was similar between polypoid lesions in diseased segments and sporadic adenomas in disease-free segments.(35, 47) Therefore, the risks of CRC in individuals with polypoid lesions, with and without IBD, can probably be considered comparable.

Large non-pedunculated colorectal polyps (LNPCPs) are defined as sessile and flat lesions with a size of ≥20 mm. LNPCP are believed to be especially at risk of progression to submucosal invasive cancer.(48) Endoscopic resection of these lesions is technically more demanding due to their large size and lack of intraluminal protrusion. This translates in a higher risk of post-resection complications and recurrence rates up to 30%.(48, 49) *En bloc* resection might overcome the drawbacks associated with standard polypectomy in these cases.(50) To date, literature concerning these lesions in the IBD population is virtually absent. Only one retrospective study reported a significant association of large polyps (defined as ≥1 cm) with the progression to advanced colorectal neoplasia (aCRN, defined as HGD or CRC).(46) Nevertheless, LNPCP can be considered

a high-risk factor in patients with IBD due to the risk of progression to submucosal invasion and the high risk of recurrence in the non-IBD population.

*Pre-resection assessment of HR-CAN*

***Statement 4: Careful examination of the colon (preferably using enhanced endoscopic imaging) should precede local excision of HR-CAN.***

***(Agreement: 100%, quality of evidence: moderate evidence)***

Pooled data showed that incidental synchronous CRC has been found in 2.7% and 13.7% of colectomy specimens of IBD patients with preoperative visible lesions, containing LGD or HGD.(51) Another study reported a pooled prevalence synchronous CRC rate of 17% in patients with UC following a preoperative diagnosis of LGD.(52) Therefore, careful examination of the entire colon is warranted prior to a local excision.

The use of high-definition white light endoscopy or (dye or virtual) chromoendoscopy instead of standard white light endoscopy is recommended.(53, 54) Add-on devices, such as distal attachment devices, to improve the adenoma detection rate (ADR) in the non-IBD setting have been studied in two recent meta-network analyses. Both studies reported a significant increase of the ADR for add-on devices as compared to standard colonoscopy.(55, 56) Although no data are available in the IBD population, add-on devices may have an additional value for the detection of (HR-)CAN as well. We suggest to use the term *enhanced endoscopic imaging* for these technologies (*i.e.,* high-definition white light endoscopy, dye or virtual chromoendoscopy). In addition, add-on devices can be considered for the detection of (HR-)CAN.

The recommendation to obtain random biopsies in the setting of (surveillance) endoscopies in the IBD population varies in the current guidelines.(1-3) Although the dysplasia yield of random biopsies during surveillance in IBD is relatively low, 12 – 20% of the dysplastic specimens were obtained via random biopsies in two recent studies.(57, 58) A large cohort study reported a greater proportions of patients with neoplasia following targeted biopsies (19.1%) as compared to random biopsies (8.2%).(59) Random biopsies have a significant yield in IBD patients with a personal history of neoplasia, concomitant primary sclerosing cholangitis or a tubular colon during colonoscopy.(58) Therefore, random biopsies are recommended in this subset of patients prior to endoscopic resection of HR-CAN.

***Statement 5:***

***A HR-CAN lesion is considered endoscopically resectable if:***

1. ***The lesion has distinct margins***
2. ***The lesion can (preferably) be removed en bloc with clear deep and lateral resection margins***

***AND there is NO evidence of***

3. ***Synchronous <u>invisible</u> dysplasia***
4. ***Moderate-to-severe inflammation of mucosa surrounding the area with HR-CAN interfering with delineation of the lesion***
5. ***Signs of deep submucosal invasion***

***(Agreement: <u>76.5%</u>, quality of evidence: <u>limited evidence</u>)***

Although current guidelines recommend to endoscopically resect visible CAN, it may be impossible to (completely) remove (HR-)CAN lesions when above criteria are not met(**Figure 3**).(1-3) Criteria for successful endoscopically resection include macroscopically identifiable, distinct margins and the absence of deep submucosal invasion (DSI)(**Figure 4**). Proper delineation of dysplasia enables a complete, preferably *en bloc* resection, thereby improving the quality and reliability of histopathologic findings.(60) Despite the use of enhanced endoscopic imaging, invisible dysplasia should be considered a contra-indication for endoscopic resection and warrants consideration of surgical resection.(61) The experts agreed that signs of DSI, such as excavation and demarcated depressed areas, are a contraindication to endoscopic resection.(62) Recently pooled data reported an overall rate of lymph node metastasis (LNM) of 11.2% in the presence of DSI in sporadic lesions (non-IBD patients). Although this meta-analysis concluded that DSI is not a strong independent predictor for LNM, a R0-resection was only achieved in 62%-65% of the polyps with DSI following ESD.(63) Data on the correlation between DSI and *en bloc*- or R0 resection rates in HR-CAN are presently lacking, but, in general, signs of DSI are considered a contra-indication for endoscopic resection in this setting. All cases of HR-CAN should be discussed at multidisciplinary team meetings prior to the endoscopic procedure, to ensure the delivery of patient-specific management.

***Statement 7: All suspected HR-CANs should be assessed according to a standardized approach and recorded in the endoscopy report. The description should include at least the following features:***

1. ***Size, delineation and location***
2. ***Description of gross morphology***
   - I. ***Granular/non-granular***
   - II. ***Paris classification***
3. ***Assessment of the pit and vascular pattern using enhanced endoscopic imaging***

***4. Assessment of endoscopic activity of the colitis in the segment, harboring the dysplastic lesion (e.g., employing the Mayo subset index, UCEIS or SES-CD)***

***(Agreement: 94.1%, quality of evidence: limited evidence)***

To date, a minimum standardized endoscopy reporting elements for CAN lesions have not been established.(60, 64, 65) Standardized endoscopy reports are crucial for clinical management decision making, to facilitate longitudinal monitoring and enable the establishment of a potential relationship between morphology and histopathology.

In line with recommendations for non-IBD-related dysplastic lesions, common endoscopic descriptors such as size, location and description of gross morphology should be included in endoscopy reports.(60, 64, 65) The delineation of the lesion should be recorded in the standardized report, to identify the lateral resection margins and enable *en bloc* resection. Furthermore, the experts agreed to include an assessment of the granularity of the lesion as non-granular type lesions have been associated with submucosal invasion, especially in the rectosigmoid.(66-68) The assessment of the Kudo pit pattern classification has shown high specificity and sensitivity (both 93%) in differentiating neoplastic lesions from non-neoplastic lesions in IBD patients.(69) In addition, a recent prospective study and a randomized controlled trial reported that pit pattern types III-V were predictive of CAN.(68, 70) Conversely, pit pattern types I-II were found to have a high negative predictive value for CAN.(70, 71) In addition, irregular vascular patterns were identified as predictors for dysplasia in IBD patients.(72) As noted previously, the presence of moderate-to-severe inflammation interferes with the detection of dysplasia and is therefore considered a contra-indication for endoscopic resection of HR-CAN. Thus, a careful assessment of the endoscopic severity of the disease using a validated endoscopic score (*e.g.,* Mayo subset index score, UCEIS and SES-CD) should be included in the endoscopy report.(1-3)

*Endoscopic resection of HR-CAN*

***Statement 8: HR-CAN should preferably be removed en bloc to lower the risk of recurrence and optimize the histological assessment. (Agreement: 94.1%, quality of evidence: limited evidence)***

Due to the higher CRC and metachronous neoplasia incidence rates following resection of non-polypoid lesions and the potential risk of deep submucosal invasion of LNPCP, an *en bloc* resection is preferred in order to lower the risk of recurrence.(1, 5, 49) Furthermore, an *en bloc* resection enables a more accurate histopathologic evaluation of the resection margins and to achieve a R0 resection.(73) Both EMR and ESD are commonly used endoscopic resection techniques allowing an *en bloc* resection. In addition, endoscopic full-thickness resection (eFTR) and endoscopic intermuscular dissection (EID), for rectal lesions with signs of DSI, are relatively new

techniques for an *en bloc* resection of colorectal lesions. Both techniques have recently been found to have high overall technical success and R0 resection rates in sporadic lesions and further experience is required to determine the role of these techniques for managing (HR-)CAN.(74, 75) Whether eFTR or EID can be successfully and safely used in (HR)-CAN is presently not clear as data for HR-CAN are not available.

A recent meta-analysis reported a pooled *en bloc* and R0 resection rate of 86% and 70%, respectively, following a hybrid endoscopic resection technique (i.e. a combination of EMR and ESD) or ESD of non-polypoid lesions with a pooled recurrence rate of 8%.(24) *En bloc* resection rates were significantly higher following ESD (93%) as compared to the hybrid technique (65%)($p<0.001$).(24) In line with these findings, pooled R0 resection rates were higher using ESD (75%) versus the hybrid technique (60%), but did not reach significance ($p=0.454$).(24) We recognize long term outcomes of these different techniques has not been published.

Piecemeal resection does not always allow complete retrieval of the lesion, which renders complete histological assessment sometimes difficult.(65) The data on piecemeal resection outcomes is conflicting. A piecemeal endoscopic mucosal resection (pEMR) has been shown to achieve excellent early and long-term outcomes for > 20 mm sporadic adenomas.(60) But piecemeal resections of sporadic non-polypoid lesions have also been associated with a pooled recurrence rate of 20% versus 3% following *en bloc* resection.(76) The recurrence rate even exceeds 30% in larger polyps (> 20 mm).(50) However, with the recent introduction of improved EMR techniques, and the use of adjuvant thermal ablation (snare tip soft coagulation or argon plasma coagulation) of the resected lesion margin, the risk of recurrence after a piecemeal resection has significantly reduced.(50, 77) Since studies in IBD patients are virtually absent, it is not clear if these results can be extrapolated to the setting of (HR-)CAN.

In conclusion, HR-CAN should preferably be removed *en bloc* to lower the risk of recurrence and optimize the histological assessment. Advanced endoscopic resection techniques should be considered for the endoscopic resection of a HR-CAN lesion. According to the current evidence, ESD has higher *en bloc* and R0 resection rates which may be a reason to prefer ESD over EMR.

***Statement 9: HR-CAN < 20 mm with good lifting (Kato I and II) can be removed using en bloc (including underwater) EMR. (Agreement: 94.1%, quality of evidence: moderate evidence)***

No statements concerning (HR-)CAN and the use of particular endoscopic resection techniques are made in the current international guideline.(60, 64, 65) Moreover, no clear cutoff point for lesion size where an *en bloc*

resection can be considered safe and feasible has been defined. The decision for an *en bloc* resection is mostly based on the morphology and size of the lesion.(65)

To date, four relatively small retrospective studies have reported outcomes on EMR in patients with CAN.(10, 11, 13, 18, 23) The outcomes of studies with a focus on resection technique (based on lesion size) were described in three studies.(10, 11, 13, 18) Nishio et al. described the results of endoscopic resection of superficial tumors in patients with UC.(10) EMR was used for the majority (62.0%) of the polyps which were predominantly <20mm (98%) and polypoid (68%). Overall *en bloc* resection rate, following EMR, was 94%. *En bloc* resection rate following EMR, as compared to ESD, did not significantly differ in polyps <20mm. *En bloc* resection rate in non-polypoid lesions was significantly higher in ESD (100%) as compared to EMR (85%) (p=0.044). Of note, documentation of presence of submucosal fibrosis was not reported.(10) Yadav et al. reported on the endoscopic treatment of polyps >10mm in IBD patients.(11) 54.8% of polyps was smaller than 20mm. The majority of polyps (95.2%) was resected using EMR yielding an *en bloc* resection rate of 70.9%.(11) A recently published, multicenter, retrospective study on the use of EMR or ESD in colitis-associated polyps (<20 mm in 90.8%) reported an overall *en bloc* rate of 63% following EMR and 65.9% following ESD.(13) All lesions with submucosal fibrosis were resected with ESD or a 'knife-assisted' resection.(13)

Based upon these results, the experts agreed that HR-CAN < 20 mm with good lifting (Kato I and II) can be removed using *en bloc* EMR. In sporadic adenomas, recent pooled data reported higher *en bloc* rates and lower recurrence rates in favor of underwater endoscopic mucosal resection (U-EMR), compared to conventional EMR.(78) The role of U-EMR has not been studied in HR-CAN, but U-EMR might be useful in the setting of these cases as well.

***Statement 10: HR-CAN < 20 mm without good lifting (Kato III and IV) or HR-CAN > 20 mm without signs of deep submucosal invasion should be removed with techniques that preferably allow en bloc resection. (Agreement: 82.4%, quality of evidence: no evidence)***

Chronic inflammation (or submucosal invasion)-related submucosal fibrosis might lead to inadequate lifting, and to incomplete resection of lesions if EMR is employed.(6, 65) ESD may overcome the limitations of EMR and should therefore be considered as a first choice to resect lesions when good lifting is not achieved.(65) The presence of concomitant submucosal fibrosis in CAN lesions is reported in the majority of studies with a range from 28.6% to 100% of the cases.(9, 12, 13, 15-20, 22, 23) In studies that report relative high frequencies of submucosal fibrosis (>60%), *en bloc* rates ranging from 78% - 100% following ESD are achieved.(12, 14-17,

19, 20, 23) Of note, the majority of these lesions were non-polypoid (76% - 100%).(12, 14-17, 19, 20, 23) Although the use of eFTR and EID has not been assessed in patients with IBD, these new techniques may prove useful in the treatment of (HR-)CAN lesions with (severe) fibrosis.(79, 80)

EMR and ESD are generally considered the preferable options for endoscopic removal of polyps, larger than 20mm, due to the limited size of the snare, difficulty to position the endoscope, and extension of the polyp over one or multiple folds.(81) Pooled data suggest that ESD results in higher *en bloc* and R0 resection rates as compared to EMR (93% vs. 65% and 75% vs. 60%, respectively) in the resection of large HR-CAN lesions (mean size of 31.4 mm).(24) No data on recurrence rates, specific to the used endoscopic resection techniques, was reported. A recent published meta-analysis reported significantly lower recurrence rates following ESD, as compared to EMR, in large (>20 mm) sporadic colorectal non-polypoid lesions.(82) Thus, ESD could be considered as the first choice of technique in the endoscopic resection of HR-CAN > 20 mm without signs of submucosal invasion due to the higher technical successes and probable lower recurrence rates.

***Statement 11: Endoscopic local excision of HR-CAN should be performed by endoscopists with sufficient skills in both EMR and ESD techniques. (Agreement: 88.2%, quality of evidence: no evidence)***

To date, no studies are available comparing the outcomes of endoscopic resection of (HR-)CAN by expert versus non-expert endoscopists. One older retrospective study by Brooker *et al.* reported that expert endoscopists had a significantly higher success rate as compared to non-experts for the resection of sporadic sessile colonic polyps.(83) The guideline of the *European Society of Gastrointestinal Endoscopy* (ESGE) recommends referring patients with non-lifting polyps without characteristics of deep submucosal invasion or lesions with high-risk features to an expert endoscopy center for evaluation, before surgery is considered.(60, 65) Furthermore, it states that large (>20 mm) sessile and laterally spreading or complex polyps should be removed by an appropriately trained and experienced endoscopist, in an appropriately resourced endoscopy center. Finally, it stipulates that ESD should be restricted to tertiary referral centers. The American Society of Gastrointestinal Endoscopy (ASGE) guideline states that referral to an expert/tertiary referral center is indicated for patients with lesions in a difficult location (e.g., appendiceal valve) or if the endoscopist is not confident about removing the lesion.(64)

Both EMR and ESD can achieve an *en bloc* resection of HR-CAN lesions. However, recent meta-analyses suggest a superiority of ESD over EMR due to higher *en bloc* and R0 resection rates in case of large non-polypoid lesions.(24) In addition, ESD should be considered first choice in case of submucosal fibrosis.

Due to the potential complexity of these procedures in patients with large non-polypoid lesions or with submucosal fibrosis, we recommend to refer patients with these kinds of lesions to centers experienced in EMR and ESD techniques.

*Outcomes and follow-up of endoscopic resection of HR-CAN*

***Statement 6: Surgical resection is indicated when HR-CAN is non-resectable. (Agreement: 100%, quality of evidence: moderate evidence)***

Non-polypoid lesions and LNPCP (i.e. HR-CAN) are associated with a high risk of (advanced) colorectal neoplasia development.(45, 46, 48) Thus, removal of these lesion types is warranted. Current international guidelines recommend surgery for endoscopically non-resectable lesions in the IBD population.(1, 3, 84) Close endoscopic surveillance or segmental resection is proposed for LGD or patients who are at high-risk for dismal postoperative outcomes.(84) A proctocolectomy is advised in case of aCRN due to the high rates of metachronous recurrence after segmental resection, based on a limited number of studies.(84) A recent multicenter retrospective study reported similar long-term survival outcomes of segmental colectomy compared to proctocolectomy.(85) Due to the risk of progression to aCRN, the type of surgical resection should be discussed with a multidisciplinary team in which other prognostic risk factors for aCRN should be taken into account.(86) If segmental resection is undertaken, continued close surveillance of residual colon is imperative.

***Statement 12:***

***Endoscopic resection should be captured by recording:***

1. ***Technical success***
    - ***I. En bloc resection***
    - ***II. R0 resection***
    - ***III. Adverse events (intra-, or post procedural bleeding, perforation, post-coagulation syndrome, need of emergency surgery, other)***
2. ***Outcomes***
    - ***I. Local recurrence at 6 months and 3 years***
    - ***II. Surgery for recurrence after 1, 3 and 5 years***

***(Agreement: 82.4%, quality of evidence: no evidence)***

Endoscopy reporting elements capturing the different aspects of technical success and outcome of endoscopic resection of (HR-)CAN lesions are currently not defined. Technical success, in non-IBD lesions, is often defined as the rate of *en bloc*- and R0-resection, and adverse events. The most common adverse events, for both EMR and ESD, comprise bleeding and perforation.(60) Although these complications can be predominantly managed

conservatively, complication-related (emergency) surgery is reported in 1%.(60) In addition, post-coagulation syndrome was considered an adverse event following endoscopic resection as the incidence varies from 1% (EMR) to 9% (ESD).(87) Due to the incidence of these complications, in combination with the potential dismal outcomes, documentation of these complications is warranted. Local recurrence (at 6 months and 3 years) and surgery for recurrence (after 1, 3 and 5 years) were proposed as outcome measures for endoscopic resection of HR-CAN.

**Statement 13:**

***The histologic report should at least include the following items:***

1. ***Size [in mm]***
2. ***Grade of dysplasia according the WHO classification***
3. ***Lateral resection margin (in mm, free if > 0.1 mm)***
4. ***Deep resection margin (in mm, free if > 0.1 mm)***

***In case of submucosal invasion:***

1. ***Maximum depth of submucosal (Sm) invasion in µm [taken from the deepest margin of the muscularis mucosae]***
2. ***Lymphatic and/or venous invasion confirmed with D2-40 immunohistochemistry***
3. ***Tumor budding (Bd1-3) according to the ITBCC***
4. ***grade of differentiation according to WHO classification***

***(Agreement: 94.1%, quality of evidence: no evidence)***

Standardization of the histologic reporting of (HR-)CAN is virtually absent in the current guidelines. A detailed pathology report containing a number of standard data elements is essential for clinical decision making and facilitates future research in this field. These standard data elements include (1) size in millimeters, (2) grade of dysplasia according to the World Health Organization and (3) both lateral and vertical/deep resection margin in millimeters.(60, 64, 65, 88) A resection margin is considered free in case of a > 1 mm free margin, based on the fact that indeterminate margins or margins < 1mm are associated with high recurrence rates of 15%-20%.(89)

In case of submucosal invasion, additional reporting on maximum depth of invasion (taken from the lowest fiber of the muscularis mucosae) and lymphatic and/or venous infiltration is recommended as it predicts LNM.(90) Tumor cell budding appears to be a promising marker for LNM as well, and has been found to have

therapeutic consequences in sporadic lesions.(90) Although the role of tumor budding in the setting of IBD is presently unclear, a recent study reported the prognostic value of tumor budding of CD-associated small bowel carcinomas.(91) Therefore, we suggest including tumor cell budding in the histology report following endoscopic resection of HR-CAN.

***Statement 14: Following complete endoscopic resection of HR-CAN, assessment of local recurrence should be performed within 3 - 6 months and annually thereafter if no residual disease is found. (Agreement: 88.2%, quality of evidence: limited evidence)***

To date, no studies have been conducted to assess the optimal follow-up strategy following endoscopic resection of CAN lesions. The ASGE endorsed guideline recommends endoscopic surveillance between 3-6 months after a complete endoscopic resection in IBD patients.(1) The ESGE recommends to perform endoscopic surveillance 3–6 months after the index treatment. If no recurrence is found, a follow-up total colonoscopy should be scheduled after 1 year.(60, 65) Following piecemeal resection or in case of positive lateral margins without an indication for surgery, colonoscopy with biopsies at 3 months is recommended.(60, 64, 65) A recently published randomized controlled trial by Nakajima *et al.* studied the optimal interval for surveillance following piecemeal resection in non-IBD patients. All patients underwent post-procedural surveillance colonoscopy at 6, 12 and 24 months. The intervention group underwent an additional colonoscopy at 3 months. No significant differences in recurrences were observed between both groups.(92) Therefore, agreement was reached that endoscopic surveillance should be performed within 3 - 6 months, and annually thereafter if no residual disease is found, following complete endoscopic resection of HR-CAN.

The lack of high-quality evidence-is the main limitation of this Delphi study. However, the methodologically rigorous and structured approach employing a 3-step voting process allowed us to achieve consensus on the important and clinically relevant issues described in this paper. The international expert panel from 12 different countries covered, in our view, the expertise relevant for the issues in question.

In conclusion, this is the first step in developing international consensus-based recommendations for endoscopic management of (HR-)CAN. Although the quality of available evidence was considered low, consensus was reached on several aspects of the management of (HR-)CAN. The present work and proposed

standardization might be a useful foundation for future studies by offering greater standardization to the approach to colorectal colitis-associated neoplasia.

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## Tables

**Table 1.** Overview of consensus statements

| Statement | Agreement grade | Quality of evidence |
|---|---|---|
| 1. We suggest to adopt the term Colitis Associated Neoplasia (CAN) for all neoplastic lesions, detected in a section of previously or presently inflamed colon. | 100% | No evidence |
| 2. (Extent of) previous or present inflammation should be/should have been confirmed by endoscopy and/or histology. | 100% | No evidence |
| 3. Non-polypoid lesions and large (>20 mm) non-pedunculated colon polyps (LNPCP) should be considered high-risk colitis-associated neoplasia (HR-CAN) | 88.2% | Limited evidence |
| 4. Careful examination of the colon (preferably using enhanced endoscopic imaging) should precede local excision of HR-CAN. | 100% | Moderate evidence |
| 5. A HR-CAN lesion is considered endoscopically resectable if:<br>1. The lesion has distinct margins<br>2. The lesion can (preferably) be removed en bloc with clear deep and lateral resection margins<br><br>AND there is NO evidence of<br>3. Synchronous invisible dysplasia<br>4. Moderate-to-severe inflammation of mucosa surrounding the area with HR-CAN interfering with delineation of the lesion<br>5. Signs of deep submucosal invasion | 76.5% | Limited evidence |
| 6. Surgical resection is indicated when HR-CAN is non-resectable. | 100% | Moderate evidence |
| 7. All suspected HR-CANs should be assessed according to a standardized approach and recorded in the endoscopy report. The description should include at least the following features:<br>1. Size, delineation and location<br>2. Description of gross morphology<br>I. Granular/non-granular<br>II. Paris classification<br>3. Assessment of the pit and vascular pattern using enhanced endoscopic imaging<br>4. Assessment of endoscopic activity of the colitis in the segment, harboring the dysplastic lesion (e.g., employing the Mayo subset index, UCEIS or SES-CD) | 94.1% | Limited evidence |
| 8. HR-CAN should preferably be removed *en bloc* to lower the risk of recurrence and optimize the histological assessment. | 94.1% | Limited evidence |
| 9. HR-CAN < 20 mm with good lifting (Kato I and II) can be removed using *en bloc* (including underwater) EMR | 94.1% | Moderate evidence |
| 10. HR-CAN < 20 mm without good lifting (Kato III and IV) or HR-CAN > 20 mm without signs of deep submucosal invasion should be removed with techniques that preferably allow *en bloc* resection. | 82.4% | No evidence |
| 11. Endoscopic local excision of HR-CAN should be performed by endoscopists with sufficient skills in both EMR and ESD techniques. | 88.2% | No evidence |
| 12. Endoscopic resection should be captured by recording:<br>1. Technical success<br>I. *En bloc* resection<br>II. R0 resection<br>III. Adverse events (intra-, or postprocedural bleeding, perforation, post-coagulation syndrome, need of emergency surgery, other)<br>2. Outcomes<br>I. Local recurrence at 6 months and 3 years<br>II. Surgery for recurrence after 1, 3 and 5 years | 82.4% | No evidence |
| 13. The histologic report should at least include the following items:<br>1. Size [mm]<br>2. Grade of dysplasia according the WHO classification<br>3. Lateral resection margin (in mm, free if > 0.1 mm)<br>4. Deep resection margin (in mm, free if > 0.1 mm)<br><br>In case of submucosal invasion:<br>1. Maximum depth of submucosal (Sm) invasion in µm [taken from the deepest margin of the muscularis mucosae]<br>2. Lymphatic and/or venous invasion confirmed with D2-40 immunohistochemistry<br>3. Tumor budding (Bd1-3) according to the ITBCC<br>4. Grade of differentiation according to WHO classification | 94.1% | No evidence |
| 14. Following complete endoscopic resection of HR-CAN, assessment of local recurrence should be performed within 3 - 6 months and annually thereafter if no residual disease is found. | 88.2% | Limited evidence |

**Abbreviations**: EMR = endoscopic mucosal resection; ESD = endoscopic submucosal dissection; ITBCC = International Tumor Budding Consensus Conference; mm= millimeters; µm = micrometers; SES-CD = Simple endoscopic score for Crohn's disease; UCEIS = Ulcerative Colitis Endoscopic Index of Severity; WHO = World Health Organization

**Figures**

**Figure 1.** Flowchart of consensus development

**Figure 2.** Flowchart after detection of high-risk colitis-associated neoplasia (HR-CAN). NB: details can be found in the statements.

**Figure 3.** In a tubular, scarred sigmoid (**Figure 3A**) of a patient with ulcerative colitis a 2,5x1,5 cm dysplastic field was identified (**Figure 3B**). The lesion could not completely be delineated. Biopsies from the surrounding normal-appearing mucosa revealed high-grade dysplasia. The patient was referred for proctocolectomy.

**Figure 4.** A 75 year old man with long-standing ulcerative colitis was referred for endoscopic resection of a 1,2x2,5cm well demarcated lesion in the rectum identified with chromoendoscopy (**Figure 4A**). The lesion was successfully resected using endoscopic submucosal dissection (**Figure 4B**). Histology revealed high-grade dysplasia.

**Supplementary material**

**Supplementary File 1.** Search strings of the PICOs

***Statement 3:***
***Non-polypoid lesions and large (>20 mm) non-pedunculated colon polyps (LNPCP) should be considered high-risk colitis-associated neoplasia (HR-CAN)***

**PICO**

| | |
|---|---|
| Question | Which polyps have the highest risk for progression to cancer in IBD? |
| P | IBD patients with non-polypoid or large (>20 mm) polyps |
| I | All polyps |
| C | A specific risk profile based on descriptive features gross morphology and (virtual) chromoendoscopy |
| O | %risk of progression to cancer, risk of metachronous CAN |

*Search string – PICO*
((Inflammatory Bowel Diseases [MeSH Terms]) OR (Inflammatory Bowel Disease*[Title/Abstract]) OR (inflammatory bowel disorder[Title/Abstract]) OR (IBD[Title/Abstract]) OR (colitis [MeSH Terms]) OR (colitis[Title/Abstract]) OR (ulcerative colitis[Title/Abstract]) OR (colitis ulcerosa[Title/Abstract]) OR (colitis, ulcerative[Title/Abstract]) OR (colitis gravis[Title/Abstract]) OR (proctocolitis[Title/Abstract]) OR (ulcerative proctocolitis[Title/Abstract]) OR (UC[Title/Abstract]) OR (Crohn Disease[Title/Abstract]) OR (Crohn's Disease[Title/Abstract]) OR (CD[Title/Abstract]) OR (inflammation AND colon[Title/Abstract]))

AND

((polyps [MeSH Terms] OR (polyp*[Title/Abstract]) OR (lesion[Title/Abstract])) AND ((non-polypoid [Title/Abstract] OR non-pedunculated [Title/Abstract] OR large [Title/Abstract] OR >20mm [Title/Abstract]) AND (Intestine, large [MeSH Terms]) OR (Large intestine [Title/Abstract]) OR (Cecum[Title/Abstract]) OR (Colon[Title/Abstract]) OR (Colon ascendens[Title/Abstract]) OR (Ascending colon[Title/Abstract]) OR (Colon descendens[Title/Abstract]) OR (Descending colon[Title/Abstract]) OR (Proximal colon[Title/Abstract]) OR (Distal colon[Title/Abstract]) OR (Sigmoid[Title/Abstract]) OR (Sigmoid colon[Title/Abstract]) OR (Rectum[Title/Abstract]) OR (Colorectal[Title/Abstract])))

AND

((Colorectal Neoplasms [MeSH Terms]) OR (colorectal neoplasm*[Title/Abstract]) OR (Intestinal Neoplasms [MeSH Terms]) OR (intestinal neoplasm*[Title/Abstract]) OR (neoplasms [MeSH Terms]) OR (neoplas*[Title/Abstract]) OR (precancerous conditions [MeSH Terms]) OR (precancerous condition*[Title/Abstract]) OR (cancer) OR (carcinoma*) OR (adenocarcinoma [MeSH Terms]) OR (adenocarcinoma*[Title/Abstract]) OR (malignancy[Title/Abstract]) OR (dysplasia[Title/Abstract]) OR (high-grade dysplasia[Title/Abstract]) OR (HGD[Title/Abstract]) OR (low-grade dysplasia[Title/Abstract]) OR (LGD[Title/Abstract]) OR (CRC[Title/Abstract]))

Hits: 2.747

***Statement 8: HR-CAN should preferably be removed en bloc to lower the risk of recurrence and optimize the histological assessment.***

**PICO**

| | |
|---|---|
| Question | Is en bloc resection preferred over a piecemeal resection for endoscopic resection of colitis-associated dysplasia? |
| P | Patients with HR-CAN in IBD |
| I | En bloc resection |
| C | Piecemeal resection |
| O | Progression to cancer, recurrence, need for surgery < 12-24 months, histological assessment |

*Search string – PICO*

((Inflammatory Bowel Diseases [MeSH Terms]) OR (Inflammatory Bowel Disease*) OR (inflammatory bowel disorder) OR (IBD) OR (colitis [MeSH Terms]) OR (colitis) OR (ulcerative colitis) OR (colitis ulcerosa) OR (colitis, ulcerative) OR (colitis gravis) OR (proctocolitis) OR (ulcerative proctocolitis) OR (UC) OR (Crohn Disease) OR (Crohn's Disease) OR (CD) OR (inflammation AND colon))

AND

((Colorectal Neoplasms [MeSH Terms]) OR (colorectal neoplasm*) OR (Intestinal Neoplasms [MeSH Terms]) OR (intestinal neoplasm*) OR (neoplasms [MeSH Terms]) OR (neoplas*) OR (precancerous conditions [MeSH Terms]) OR (precancerous condition*) OR (cancer) OR (carcinoma*) OR (adenocarcinoma [MeSH Terms]) OR (adenocarcinoma*) OR (malignancy) OR (dysplasia) OR (high-grade dysplasia) OR (HGD) OR (low-grade dysplasia) OR (LGD) OR (CRC))

AND

((en bloc resection) AND ((endoscopic mucosal resection) OR (EMR) OR (endoscopic submucosal dissection) OR (ESD) OR (endoscopic full thickness resection) OR (eFTR))

AND

(((piecemeal) AND (endoscopic mucosal resection) OR (EMR) OR (endoscopic resection)) OR (pEMR) OR (snare) OR (polypectomy)))

Hits: 29

***Statement 9: HR-CAN < 20 mm with good lifting (Kato I and II) can be removed using en bloc (including underwater) EMR.***

**PICO**

| | |
|---|---|
| Question | Can en bloc (underwater) EMR be performed for HR-CAN < 20 mm with good lifting (Kato I and II)? |
| P | Patients with HR-CAN < 20 mm with good lifting (Kato I and II) |
| I | En bloc (underwater) EMR |
| C | Other techniques of resection |
| O | Progression to cancer, recurrence, need for surgery < 12-24 months, histological assessment |

*Search string – PICO*
((Inflammatory Bowel Diseases [MeSH Terms]) OR (Inflammatory Bowel Disease*) OR (inflammatory bowel disorder) OR (IBD) OR (colitis [MeSH Terms]) OR (colitis) OR (ulcerative colitis) OR (colitis ulcerosa) OR (colitis, ulcerative) OR (colitis gravis) OR (proctocolitis) OR (ulcerative proctocolitis) OR (UC) OR (Crohn Disease) OR (Crohn's Disease) OR (CD) OR (inflammation AND colon))

AND

((Colorectal Neoplasms [MeSH Terms]) OR (colorectal neoplasm*) OR (Intestinal Neoplasms [MeSH Terms]) OR (intestinal neoplasm*) OR (neoplasms [MeSH Terms]) OR (neoplas*) OR (precancerous conditions [MeSH Terms]) OR (precancerous condition*) OR (cancer) OR (carcinoma*) OR (adenocarcinoma [MeSH Terms]) OR (adenocarcinoma*) OR (malignancy) OR (dysplasia) OR (high-grade dysplasia) OR (HGD) OR (low-grade dysplasia) OR (LGD) OR (CRC))

AND

((en bloc resection) AND ((endoscopic mucosal resection) OR (EMR) OR (UEMR)))

AND

((good lifting) OR (Kato I) OR Kato (II) OR (lifting) OR submucosal fibrosis))

Hits: 9

***Statement 10: HR-CAN < 20 mm without good lifting (Kato III and IV) or HR-CAN > 20 mm without signs of deep submucosal invasion should be removed with techniques that preferably allow en bloc resection.***

**PICO**

| | |
|---|---|
| Question | Can *en bloc* be performed for HR-CAN < 20 mm without good lifting (Kato III and IV) or HR-CAN > 20 mm without signs of deep submucosal invasion? |
| P | Patients with HR-CAN < 20 mm without good lifting (Kato III and IV) or HR-CAN > 20 mm without signs of deep submucosal invasion |
| I | Techniques allowing *en bloc* resection |
| C | Other techniques of resection |
| O | Progression to cancer, recurrence, need for surgery < 12-24 months, histological assessment |

*Search string – PICO*
((Inflammatory Bowel Diseases [MeSH Terms]) OR (Inflammatory Bowel Disease*) OR (inflammatory bowel disorder) OR (IBD) OR (colitis [MeSH Terms]) OR (colitis) OR (ulcerative colitis) OR (colitis ulcerosa) OR (colitis, ulcerative) OR (colitis gravis) OR (proctocolitis) OR (ulcerative proctocolitis) OR (UC) OR (Crohn Disease) OR (Crohn's Disease) OR (CD) OR (inflammation AND colon))

AND

((Colorectal Neoplasms [MeSH Terms]) OR (colorectal neoplasm*) OR (Intestinal Neoplasms [MeSH Terms]) OR (intestinal neoplasm*) OR (neoplasms [MeSH Terms]) OR (neoplas*) OR (precancerous conditions [MeSH Terms]) OR (precancerous condition*) OR (cancer) OR (carcinoma*) OR (adenocarcinoma [MeSH Terms]) OR (adenocarcinoma*) OR (malignancy) OR (dysplasia) OR (high-grade dysplasia) OR (HGD) OR (low-grade dysplasia) OR (LGD) OR (CRC))

AND

((en bloc resection) OR (endoscopic submucosal dissection) OR (ESD) OR (EMR))

AND

((non-lifting) OR (Kato III) OR Kato (IV) OR (lifting) OR submucosal fibrosis))

Hits: 17

***Statement 11: Endoscopic local excision of HR-CAN should be performed by endoscopists with sufficient skills in both EMR and ESD techniques.***

**PICO**

| | |
|---|---|
| Question | Should endoscopic resection of HR-CAN be formed by skilled/expert endoscopists? |
| P | Patients with HR-CAN suitable for endoscopic resection |
| I | Skilled/expert endoscopists |
| C | All endoscopists |
| O | Progression to cancer, recurrence, need for surgery < 12-24 months, histological assessment |

*Search string – PICO*
((Inflammatory Bowel Diseases [MeSH Terms]) OR (Inflammatory Bowel Disease*[Title/Abstract]) OR (inflammatory bowel disorder[Title/Abstract]) OR (IBD[Title/Abstract]) OR (colitis [MeSH Terms]) OR (colitis[Title/Abstract]) OR (ulcerative colitis[Title/Abstract]) OR (colitis ulcerosa[Title/Abstract]) OR (colitis, ulcerative[Title/Abstract]) OR (colitis gravis[Title/Abstract]) OR (proctocolitis[Title/Abstract]) OR (ulcerative proctocolitis[Title/Abstract]) OR (UC[Title/Abstract]) OR (Crohn Disease[Title/Abstract]) OR (Crohn's Disease[Title/Abstract]) OR (CD[Title/Abstract]) OR (inflammation AND colon[Title/Abstract]))

AND

((Colorectal Neoplasms [MeSH Terms]) OR (colorectal neoplasm* [Title/Abstract]) OR (Intestinal Neoplasms [MeSH Terms]) OR (intestinal neoplasm*) OR (neoplasms [MeSH Terms]) OR (neoplas*) OR (precancerous conditions [MeSH Terms]) OR (precancerous condition*) OR (cancer) OR (carcinoma*) OR (adenocarcinoma [MeSH Terms]) OR (adenocarcinoma*) OR (malignancy) OR (dysplasia) OR (high-grade dysplasia) OR (HGD) OR (low-grade dysplasia) OR (LGD) OR (CRC))

AND

((skilled) OR (expert) OR (skilled endoscopist*) OR (expert endoscopist*) OR (tertiary referral center) OR (expert center))

AND

((en bloc resection) AND ((endoscopic mucosal resection) OR (EMR) OR (endoscopic submucosal dissection) OR (ESD) OR (endoscopic full thickness resection) OR (eFTR) OR (piecemeal) AND (endoscopic mucosal resection) OR (EMR) OR (endoscopic resection) OR (pEMR) OR (snare) OR (polypectomy))

Hits: 3

**PICO**

| | |
|---|---|
| Question | Can en bloc resection be performed for HR-CAN > 20 mm without signs of deep submucosal invasion? |
| P | Patients with HR-CAN > 20 mm without signs of deep submucosal invasion |
| I | *En bloc resection* |
| C | Other techniques of resection |
| O | Progression to cancer, recurrence, need for surgery < 12-24 months, histological assessment |

*Search string – PICO*
((Inflammatory Bowel Diseases [MeSH Terms]) OR (Inflammatory Bowel Disease*) OR (inflammatory bowel disorder) OR (IBD) OR (colitis [MeSH Terms]) OR (colitis) OR (ulcerative colitis) OR (colitis ulcerosa) OR (colitis, ulcerative) OR (colitis gravis) OR (proctocolitis) OR (ulcerative proctocolitis) OR (UC) OR (Crohn Disease) OR (Crohn's Disease) OR (CD) OR (inflammation AND colon))

AND

((Colorectal Neoplasms [MeSH Terms]) OR (colorectal neoplasm*) OR (Intestinal Neoplasms [MeSH Terms]) OR (intestinal neoplasm*) OR (neoplasms [MeSH Terms]) OR (neoplas*) OR (precancerous conditions [MeSH Terms]) OR (precancerous condition*) OR (cancer) OR (carcinoma*) OR (adenocarcinoma [MeSH Terms]) OR (adenocarcinoma*) OR (malignancy) OR (dysplasia) OR (high-grade dysplasia) OR (HGD) OR (low-grade dysplasia) OR (LGD) OR (CRC))

AND

((en bloc resection) OR (endoscopic submucosal dissection) OR (ESD))

AND

((large polyp*) OR (> 20 millimetres) OR (>20 mm))

Hits: 46

**Supplementary File 2.** Detailed overview of the third and final round of voting for consensus agreement (n=17) and assessment of quality of evidence (n=15)

**Statement 1**: We suggest to adopt the term Colitis Associated Neoplasia (CAN) for all neoplastic lesions, detected in a section of previously or presently inflamed colon.

| | |
|---|---|
| Strongly disagree | 0% |
| Disagree | 0% |
| Neutral | 0% |
| Agree | 52.9% |
| Strongly agree | 47.1% |

| | |
|---|---|
| No evidence | 40% |
| Conflicting evidence | 6.7% |
| Limited evidence | 33.3% |
| Moderate evidence | 20% |
| Strong evidence | 0% |

*Agreement:* 100%
*Quality of evidence*: no evidence

**Statement 2**: Extent of previous or present inflammation should be/should have been confirmed by endoscopy and/or histology.

| | |
|---|---|
| Strongly disagree | 0% |
| Disagree | 0% |
| Neutral | 0% |
| Agree | 76.5% |
| Strongly agree | 23.5% |

| | |
|---|---|
| No evidence | 33.3% |
| Conflicting evidence | 13.3% |
| Limited evidence | 26.7% |
| Moderate evidence | 26.7% |
| Strong evidence | 0% |

*Agreement:* 100%
*Quality of evidence*: no evidence

**Statement 3**: Non-polypoid lesions and large (>20 mm) non-pedunculated colon polyps (LNPCP) should be considered high-risk colitis-associated neoplasia (HR-CAN)

| | |
|---|---|
| Strongly disagree | 0% |
| Disagree | 5.9% |
| Neutral | 5.9% |
| Agree | 58.8% |
| Strongly agree | 29.4% |

| | |
|---|---|
| No evidence | 20% |
| Conflicting evidence | 20% |
| Limited evidence | 40% |
| Moderate evidence | 20% |
| Strong evidence | 0% |

*Agreement:* 88.2%
*Quality of evidence:* limited evidence

**Statement 4**: Careful examination of the colon (preferably using enhanced endoscopic imaging) should precede local excision of HR-CAN.

| | |
|---|---|
| Strongly disagree | 0% |
| Disagree | 0% |
| Neutral | 0% |
| Agree | 17.6% |
| Strongly agree | 82.4% |

| | |
|---|---|
| No evidence | 6.7% |
| Conflicting evidence | 6.7% |
| Limited evidence | 13.3% |
| Moderate evidence | 60% |
| Strong evidence | 13.3% |

*Agreement:* 100%
*Quality of evidence*: moderate evidence

**Statement 5:**
A HR-CAN lesion is considered endoscopically resectable if:

1. The lesion has distinct margins
2. The lesion can (preferably) be removed en bloc with clear deep and lateral resection margins

AND there is NO evidence of

3. Synchronous invisible dysplasia
4. Moderate-to-severe inflammation of mucosa surrounding the area with HR-CAN interfering with delineation of the lesion
5. Signs of deep submucosal invasion

| | |
|---|---|
| Strongly disagree | 0% |
| Disagree | 23.5% |
| Neutral | 0% |
| Agree | 47.1% |
| Strongly agree | 29.4% |

| | |
|---|---|
| No evidence | 20% |
| Conflicting evidence | 0% |
| Limited evidence | 46.6% |
| Moderate evidence | 26.7% |
| Strong evidence | 6.7% |

*Agreement:* 76.5%
*Quality of evidence*: limited evidence

**Statement 6**: Surgical resection is indicated when HR-CAN is non-resectable.

| | |
|---|---|
| Strongly disagree | 0% |
| Disagree | 0% |
| Neutral | 0% |
| Agree | 47.1% |
| Strongly agree | 52.9% |

| | |
|---|---|
| No evidence | 26.7% |
| Conflicting evidence | 0% |
| Limited evidence | 20% |
| Moderate evidence | 40% |
| Strong evidence | 13.3% |

*Agreement:* 100%

*Quality of evidence*: moderate evidence

**Statement 7:**

All suspected HR-CANs should be assessed according to a standardized approach and recorded to the endoscopy report. The description should include at least the following features:

1. Size, delineation and location
2. Description of gross morphology
    I. Granular/non-granular
    II. Paris classification
2. Assessment of the pit and vascular pattern using enhanced endoscopic imaging
3. Assessment of endoscopic activity of the colitis in the segment, harboring the dysplastic lesion (*e.g.,* employing the Mayo subset index, UCEIS or SES-CD)

| | |
|---|---|
| Strongly disagree | 0% |
| Disagree | 0% |
| Neutral | 5.9% |
| Agree | 41.2% |
| Strongly agree | 52.9% |

| | |
|---|---|
| No evidence | 26.7% |
| Conflicting evidence | 0% |
| Limited evidence | 33.3% |
| Moderate evidence | 33.3% |
| Strong evidence | 6.7% |

*Agreement:* 94.1%
*Quality of evidence*: limited evidence

**Statement 8**: HR-CAN should preferably be removed *en bloc* to lower the risk of recurrence and optimize the histological assessment.

| | |
|---|---|
| Strongly disagree | 0% |
| Disagree | 0% |
| Neutral | 5.8% |
| Agree | 47.1% |
| Strongly agree | 47.1% |

| | |
|---|---|
| No evidence | 26.7% |
| Conflicting evidence | 6.6% |
| Limited evidence | 40% |
| Moderate evidence | 26.7% |
| Strong evidence | 0% |

*Agreement:* 94.1%
*Quality of evidence*: limited evidence

**Statement 9**: HR-CAN < 20 mm with good lifting (Kato I and II) can be removed using en bloc (including underwater) EMR

| | |
|---|---|
| Strongly disagree | 0% |
| Disagree | 0% |
| Neutral | 5.9% |
| Agree | 76.5% |
| Strongly agree | 17.6% |

| | |
|---|---|
| No evidence | 20% |
| Conflicting evidence | 6.7% |
| Limited evidence | 40% |
| Moderate evidence | 33.3% |
| Strong evidence | 0% |

*Agreement:* 94.1%
*Quality of evidence*: moderate evidence

**Statement 10**: HR-CAN < 20 mm without good lifting (Kato III and IV) or HR-CAN > 20 mm without signs of deep submucosal invasion should be removed with techniques that preferably allow en bloc resection.

| | |
|---|---|
| Strongly disagree | 5.9% |
| Disagree | 0% |
| Neutral | 11.8% |
| Agree | 47.1% |
| Strongly agree | 35.3% |

| | |
|---|---|
| No evidence | 40% |
| Conflicting evidence | 6.7% |
| Limited evidence | 20% |
| Moderate evidence | 33.3% |
| Strong evidence | 0% |

*Agreement:* 82.4%
*Quality of evidence*: no evidence

**Statement 11**: Endoscopic local excision of HR-CAN should be performed by endoscopists with sufficient skills in both EMR and ESD techniques.

| | |
|---|---|
| Strongly disagree | 5.9% |
| Disagree | 0% |
| Neutral | 5.9% |
| Agree | 29.4% |
| Strongly agree | 58.8% |

| | |
|---|---|
| No evidence | 40% |
| Conflicting evidence | 6.7% |
| Limited evidence | 40% |
| Moderate evidence | 13.3% |
| Strong evidence | 0% |

*Agreement:* 88.2%
*Quality of evidence*: no evidence

**Statement 12**:
Endoscopic resection should be captured by recording:

1. Technical success
    - I. *En* bloc resection
    - II. R0 resection
    - III. Adverse events (intra-, or postprocedural bleeding, perforation, post-coagulation syndrome, need of emergency surgery, other)

2. Outcomes
    - I. Local recurrence at 6 months and 3 years
    - II. Surgery for recurrence after 1, 3 and 5 years

| | |
|---|---|
| Strongly disagree | 0% |
| Disagree | 11.8% |
| Neutral | 5.9% |
| Agree | 58.9% |
| Strongly agree | 23.5% |

| | |
|---|---|
| No evidence | 53.3% |
| Conflicting evidence | 0% |
| Limited evidence | 53.3% |
| Moderate evidence | 6.6% |
| Strong evidence | 0% |

*Agreement:* 82.4%
*Quality of evidence*: no evidence

**Statement 13:**

The histologic report should at least include the following items:

1. Size [in mm]
2. Grade of dysplasia according the WHO classification
3. Lateral resection margin (in mm, free if > 0.1 mm)
4. Deep resection margin (in mm, free if > 0.1 mm)

In case of submucosal invasion:

1. Maximum depth of submucosal (Sm) invasion in µm [taken from the deepest margin of the muscularis mucosae]
2. Lymphatic and/or venous invasion confirmed with D2-40 immunohistochemistry
3. Tumor budding (Bd1-3) according to the ITBCC
4. Grade of differentiation according to WHO classification

| | |
|---|---|
| Strongly disagree | 0% |
| Disagree | 5.9% |
| Neutral | 0% |
| Agree | 52.9% |
| Strongly agree | 41.2% |

| | |
|---|---|
| No evidence | 33.3% |
| Conflicting evidence | 13.4% |
| Limited evidence | 26.7% |
| Moderate evidence | 13.3% |
| Strong evidence | 13.3% |

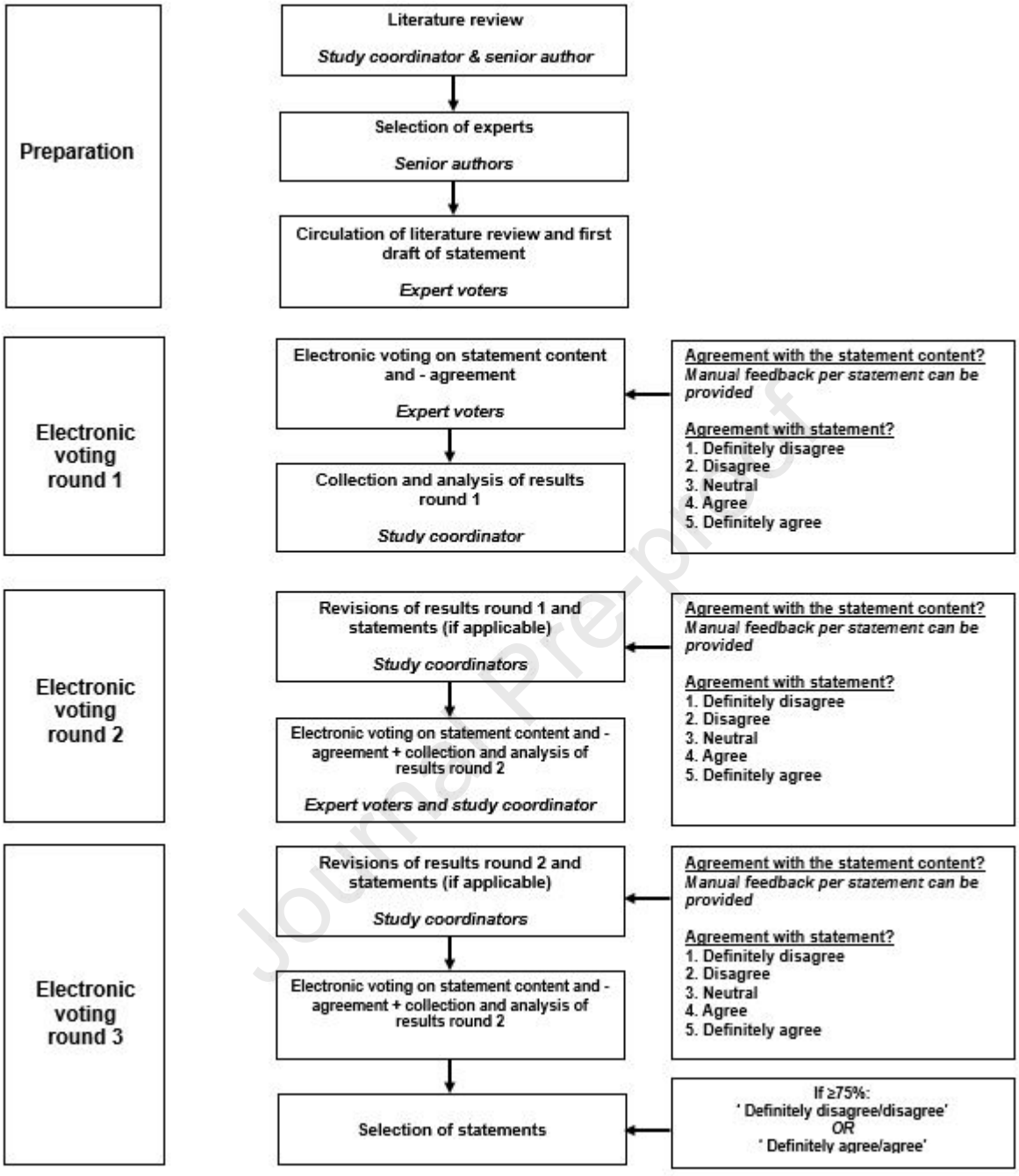
*Agreement:* 94.1%
*Quality of evidence*: no evidence

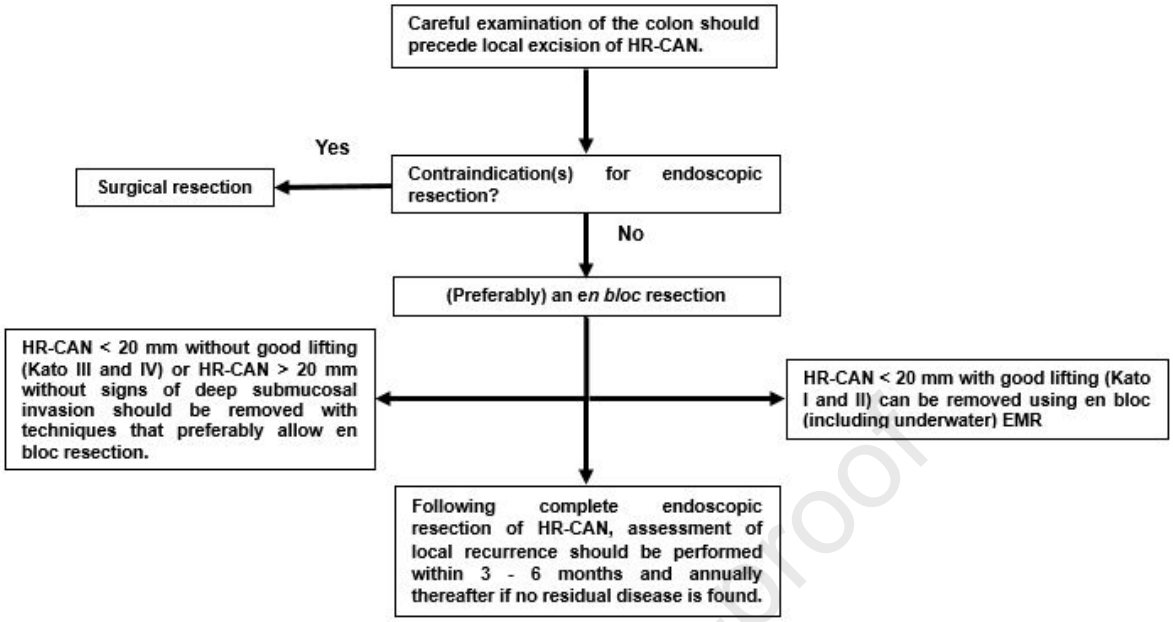
**Statement 14**: Following complete endoscopic resection of HR-CAN, assessment of local recurrence should be performed within 3 - 6 months and annually thereafter if no residual disease is found.

| | |
|---|---|
| Strongly disagree | 0% |
| Disagree | 0% |
| Neutral | 11.8% |
| Agree | 64.7% |
| Strongly agree | 23.5% |

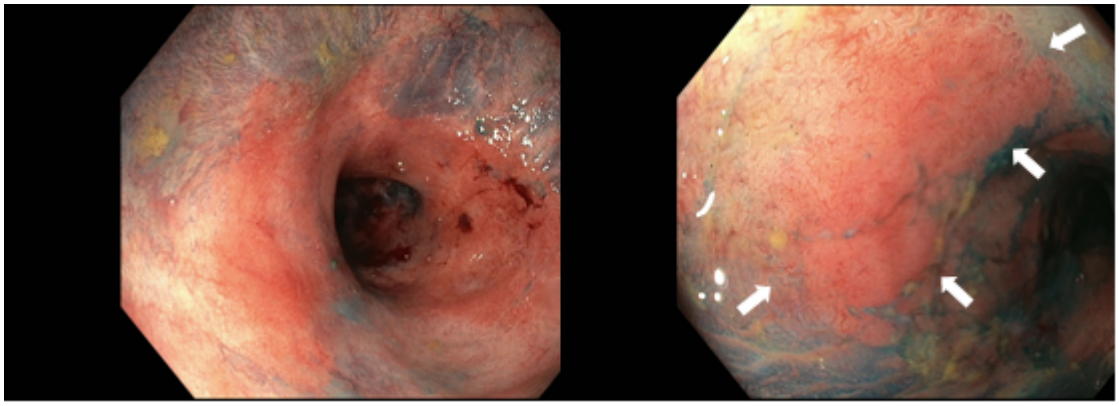
| | |
|---|---|
| No evidence | 33.3% |
| Conflicting evidence | 0% |
| Limited evidence | 46.7% |
| Moderate evidence | 20% |
| Strong evidence | 0% |

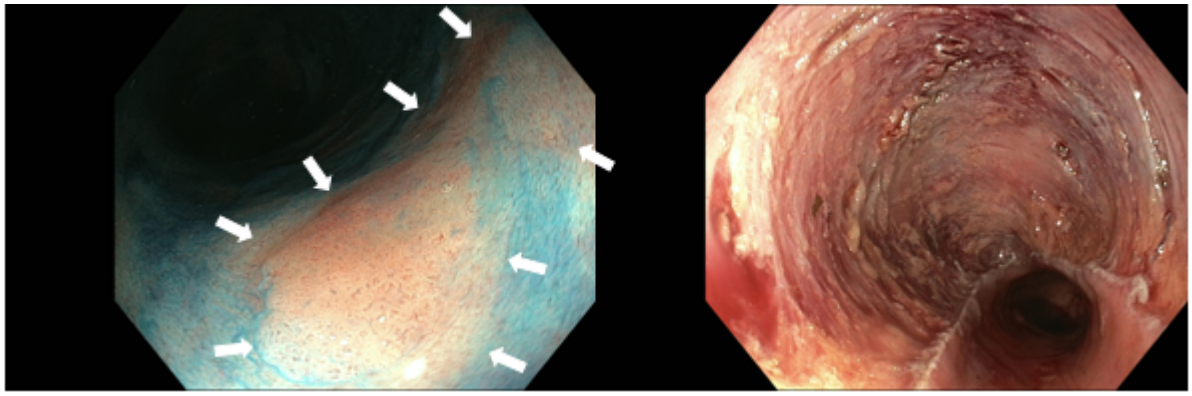
*Agreement:* 88.2%
*Quality of evidence*: limited evidence






**Abbreviations**: HR-CAN = high-risk colitis associated neoplasia; EMR = endoscopic mucosal resection





**Abbreviations**

Inflammatory bowel disease (IBD); colitis-associated neoplasia (CAN); endoscopic mucosal resection (EMR); endoscopic submucosal dissection (ESD); ulcerative colitis (UC); colorectal cancer (CRC); high-grade dysplasia (HGD); Crohn's disease (CD); ulcerative colitis endoscopic index of severity (UCEIS); the ulcerative colitis colonoscopic index of severity (UCCIS); Crohn's disease endoscopic index of severity (CDEIS); simple endoscopic score for Crohn's disease (SES-CD); high-risk colitis-associated neoplasia (HR-CAN); low-grade dysplasia (LGD); Large non-pedunculated colorectal polyps (LNPCPs); colorectal neoplasia (CRN); adenoma detection rate (ADR); deep submucosal invasion (DSI); lymph node metastasis (LNM); endoscopic full-thickness resection (eFTR); endoscopic intermuscular dissection (EID); piecemeal endoscopic mucosal resection (pEMR); underwater endoscopic mucosal resection (U-EMR); European Society of Gastrointestinal Endoscopy (ESGE); American Society of Gastrointestinal Endoscopy (ASGE); advanced colorectal neoplasia (aCRN)