Screening for dysplasia in inflammatory bowel diseases

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Surveillance

Why and when do we do surveillance?

ECCO statement 8A
The risk of colorectal cancer in ulcerative colitis is increased compared to the general population. Risk is associated with disease duration [EL 2], extent [EL 2] and more severe or persistent inflammatory activity [EL 2]

ECCO statement 8B
Concomitant primary sclerosing cholangitis [EL 2] and a family history of colorectal cancer [EL 3] confer an additional risk for colorectal cancer

ECCO statement 8D (adapted from statement 13D, Annese et al)
Screening colonoscopy should be offered eight years following the onset of symptoms to all patients to reassess disease extent and exclude dysplasia [EL 5]

ECCO statement 8F
In patients with concurrent primary sclerosing cholangitis, annual surveillance colonoscopy should be performed following the diagnosis of primary sclerosing cholangitis, irrespective of disease activity, extent and duration [EL3]

The multistep endoscopic approach in IBD dysplasia
The multistep endoscopy approach in IBD dysplasia

Detection
Characterisation
Treatment
Follow-up
### ECCO Statement 8I:

Surveillance colonoscopy should take into account **local expertise**. **Chromoendoscopy with targeted biopsies** has been shown to increase dysplasia detection rate [EL2]. Alternatively, random biopsies [quadrantic biopsies every 10 cm] and targeted biopsies of any visible lesion should be performed if white light endoscopy is used [EL3]. High-definition endoscopy should be used if available.

### SCENIC Statement 3:

When performing surveillance with **high-definition colonoscopy**, **chromoendoscopy** is suggested rather than white-light colonoscopy. (84% agreement; conditional recommendation; low-quality evidence)

RR: **1.8** (1.2-2.6).
Absolute risk increase: **6%** (3%-9%)

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**ECCO-ESGAR guideline Maaser C et al J Crohn Colitis 2019 ;13:144-164**

During the procedure

Control of bowel inflammation

If there is activity present dye-spray chromoendoscopy cannot be used


During the procedure

• Assess bowel preparation:
  • Boston Bowel Preparation Scale: ≥6 total score (at least 2 in each segment 2+2+2)
    • Assess each segment: Left colon, Transverse colon and Right colon
    • 0 points: Segment unprepared colon with mucosa not visualized by the presence of solid stool
    • 1 point: Areas colon segment seen by the presence of fecal liquid and semisolid
    • 2 points: Low fecal liquid content, allows good visualization of the mucosa
    • 3 points: Excellent visualization of the mucosa without the presence of liquid remains
  
  • Aronchick Scale:
    • Excellent: Small volume of clear liquid or >95% of surface seen
    • Good: Large volume of clear liquid covering 5-25% of surface but >90% of surface seen
    • Fair: Some semisolid stool that can be suctioned or washed away but >90% of surface seen
    • Poor: Some semisolid stool that can be suctioned or washed away but <90% of surface seen
    • Inadequate: Solid stool that impedes the vision

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  • Inadequate: Solid stool that impedes the vision

Dye-spray chromoendoscopy can be used

Megna B et al GIE 2018;89:373-379
1. Prepare the Dye solution

- **Indigo carmine** (0.8%, 5ml ampule): 2 ampules + 250 ml water (0.03%)
- **Methylene blue** (1%, 10ml ampule): 1 ampule + 240ml water (0.04%)

2. Connect the bottle with the dye to the scope

3. Use the pump-jet with your feet

4. Spray the dye with clock/anti-clockwise movements

**Surveillance**

**Dye Chromoendoscopy Technique**


1. Prepare the Dilution

- **Indigo Carmine** (0.8%, 5ml ampule): 2 ampules + 250 ml water (0.03%)
- **Methylene Blue** (1%, 10ml ampule): 1 ampule + 240 ml water (0.04%)

2. Put the catheter in the channel of the probe

3. Fill a syringe of 100 ml

4. Catheter should protrude 2-3 cm from the endoscope. Use segmental and rotational technique

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**Surveillance**

**Dye Chromoendoscopy Technique**

**ECCO-ESGAR guideline** Maaser C et al J Crohn Colitis 2019;13:144-164

In a randomized controlled trial, Targeted biopsy and random biopsies detect similar proportions of neoplasia. However, a targeted biopsy appears to be more cost-effective method.

Watanabe T et al Gastroenterology 2016; 151; 1122

Moussata D et al Gut 2018; 616-624
Withdrawal time have been clearly shown to be associated with improved adenoma detection in non-colitis patients (likely the same in IBD surveillance).

At least 8-10 minutes should be taken for an accurate inspection of the colonic mucosa.

Remove endoscopically resectable suspicious lesions by using polypectomy or endoscopic mucosal resection.

Do targeted biopsies of any unresectable abnormality visualized through chromoendoscopy to diagnose dysplasia.

Iacucci et al Gut 2018
Do biopsies of flat area surrounding lesions to assess for dysplasia.

Consider tattoo of suspicious dysplastic lesions arising from flat mucosa or not amenable to complete removal.

Barriers

- Training
- Unknown Learning curve
- Time requirement
- Billing

Barriers

- Lack of risk stratification
- Uncertainty of appropriate surveillance intervals

If you do not perform chromoendoscopy in the majority of your cases (>50%), what is the reason?

- Difficulty getting agent: 27%
- Insufficient training: 32%
- Not recommended by U.S. professional society guidelines: 22%
- Believe it's ineffective: 14%
- Not reimbursable: 5%
Keys strategies to implement DCE

- **Endoscopic unit**
  - Endoscopists
  - Training

- Dedicated a longer slot to DCE (at least 45 minutes, more for the training)
- Trained nurses in DCE
- Reserve high definition instruments to DCE
- Provide necessary tools to perform DCE (catheter spray, pump-jet, dye)
- Experienced dedicated nurses for EMR or ESD

*Sanduleanu S et al GIE 2016; 83: 213-22*
Keys strategies to improve quality performance

- Endoscopic unit

- Endoscopists

- Training

- Be aware of the type of endoscope

- Be familiar with the different types of dyes (methylene blue and indigo carmine) and their concentrations

- Be familiar with the method of application (pump-jet, catheter spray)

- Be aware of how many and where biopsies should be taken

- Paris and Kudo pit pattern classification

Sanduleanu S et al GIE 2016; 83: 213-22
Keys strategies to implement training

- **Endoscopic unit**

- **Endoscopists**

- **Training**

  - Self-training and e-learning (online resources, websites, videos, pictures)
  - Development of validated and standardized training modules
  - Perform the first 5 dye spraying colonoscopies with expert endoscopists
  - EMR and ESD for IBD surveillance requires considerable specialised training in expert centres

*Sanduleanu S et al GIE 2016; 83: 213-22*
WHAT’S THE FUTURE?

Dye chromoendoscopy or Dyeless chromoendoscopy?
Virtual Chromoendoscopy (VCE)

• There is no significant difference in the detection of lesions in IBD patients between NBI and DCE.

• NBI is timesaver and easier than DCE and may replace DCE in the future for surveillance of long-standing UC.

• HD-WL and VCE with iSCAN are not inferior to DCE for detection of colonic neoplastic lesions.

• HD-WL and VCE may replace DCE in the future.


Iacucci M et al Amer J Gastroenterol 2018; 113: 225-234.
Conclusion: This is the first RCT to include validated PE in a colitis surveillance program. **VCE is safe, technically easier, quicker and more comfortable test, with dysplasia detection at least as good as that of CE, overcoming many barriers to the wider adoption of CE.** This trial may serve as a successful foundation for a multicenter trial to confirm the value of VCE for colitis surveillance.
Characterization of the colonic lesions?
During the procedure

Dye Chromoendoscopy

**CHARACTERIZATION-IF LESION DETECTED**

<table>
<thead>
<tr>
<th>Indigo carmine (0.8%, 5 ml ampule)</th>
<th>Water 25 ml</th>
<th>Dye solution (Indigo carmine 0.13%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylene blue (1%, 10 ml ampule)</td>
<td>Water 40 ml</td>
<td>Dye solution (Methylene Blue 0.2%)</td>
</tr>
</tbody>
</table>

Fill a syringe with the dye solution

Spray the syringe through biopsy channel directly on the lesion


Characterization of the colonic lesion

Paris classification + Borders + Ulceration + Kudo pit pattern

Figure 3. SCENIC classification of inflammatory bowel disease colorectal dysplasia.

Characterization of the colonic lesions

Problems with Kudo Pit Pattern:

- Inflammatory activity may mimic neoplasia

- However, it should be noted that regenerative changes masquerade as dysplastic ones even in histopathology

- Serrated sessile adenomas (SSA) often have regular pit pattern-similar appearances as HP


Regenerative mucosal pattern
Characterization of the colonic lesions

- Kudo pit pattern seems to have high accuracy to characterize the colonic lesions.

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Table 4. Endoscopic features predictive of dysplasia. Results of univariate and multivariate analyses

<table>
<thead>
<tr>
<th>Endoscopic characteristic</th>
<th>Non-dysplasia</th>
<th>Dysplasia</th>
<th>p Value</th>
<th>OR (CI 95%)</th>
<th>Adjusted p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size in millimetres, median (Q10)</td>
<td>4 (3-6)</td>
<td>5 (3-6)</td>
<td>0.850</td>
<td>1.01 (0.96 to 1.06)</td>
<td>–</td>
</tr>
<tr>
<td>Located at proximal colon%</td>
<td>43.7</td>
<td>58.5</td>
<td>0.008</td>
<td>1.86 (1.02 to 3.40)</td>
<td>0.041</td>
</tr>
<tr>
<td>Distending lesion%</td>
<td>79</td>
<td>59.4</td>
<td>0.004</td>
<td>2.80 (1.57 to 5.08)</td>
<td>0.001</td>
</tr>
<tr>
<td>Neoplastic Kudo pit pattern%</td>
<td>82</td>
<td>32.1</td>
<td>0.001</td>
<td>5.05 (2.56 to 9.88)</td>
<td>0.001</td>
</tr>
<tr>
<td>Loss of intramucosal lines%</td>
<td>43.5</td>
<td>56.4</td>
<td>0.022</td>
<td>1.95 (1.06 to 3.50)</td>
<td>0.003</td>
</tr>
<tr>
<td>Haeckey%</td>
<td>4.9</td>
<td>3.9</td>
<td>0.172</td>
<td>0.60 (0.29 to 1.25)</td>
<td>0.211</td>
</tr>
<tr>
<td>Irregular morphology%</td>
<td>14.9</td>
<td>9.6</td>
<td>0.172</td>
<td>0.60 (0.29 to 1.25)</td>
<td>0.211</td>
</tr>
<tr>
<td>Poorly demarcated%</td>
<td>8.2</td>
<td>4.3</td>
<td>0.074</td>
<td>0.36 (0.14 to 0.92)</td>
<td>0.036</td>
</tr>
<tr>
<td>Abnormal vascularity%</td>
<td>4.4</td>
<td>4.3</td>
<td>0.99</td>
<td>0.33 (2.90)</td>
<td>1.00</td>
</tr>
<tr>
<td>Utecentrated surface%</td>
<td>5.1</td>
<td>7.1</td>
<td>0.133</td>
<td>2.33 (0.69 to 8.11)</td>
<td>0.211</td>
</tr>
<tr>
<td>Carcin lesion%</td>
<td>2.6</td>
<td>1.1</td>
<td>0.172</td>
<td>0.50 (0.17 to 1.42)</td>
<td>0.211</td>
</tr>
</tbody>
</table>

Table 5. Multivariate analysis: endoscopic findings predictive of dysplasia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (0.99–1.08)</td>
</tr>
<tr>
<td>Paris class</td>
<td>3.30 (1.26–8.96)</td>
</tr>
<tr>
<td>Kudo pit pattern (II, III–V)</td>
<td>21.50 (8.65–60.10)</td>
</tr>
<tr>
<td>Localization: left colon</td>
<td>1.14 (0.33–3.88)</td>
</tr>
<tr>
<td>Localization: right colon</td>
<td>6.52 (1.98–22.5)</td>
</tr>
</tbody>
</table>

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Carballal et al. Gut 2016; 67:70-78

Iacucci et al. Am J Gastroenterol 2018; 113: 225-234
Characterization of the colonic lesions

- Kudo pit patterns I and II vs IIIL-IV-IIIS-V have an accuracy to predict histological dysplasia of 70%, sensitivity of 68% and negative predictive value (NPV) of 88%.

- Similar data are obtained with DCE and VCE (NBI).

- However, DCE has a better sensitivity and a positive predictive value (PPV).

**Table 2. Accuracy to predict histologic-proven neoplastic lesion**

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n = 50)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-III vs II-IIIS-V</td>
<td>77% (54%-85%)</td>
<td>83% (51%-94%)</td>
<td>88% (84%-94%)</td>
<td>46% (36%-61%)</td>
<td>70% (58%-82%)</td>
</tr>
<tr>
<td>Non-neoplastic vs nonplastic</td>
<td>77% (31%-100%)</td>
<td>69% (43%-92%)</td>
<td>90% (75%-100%)</td>
<td>48% (37%-67%)</td>
<td>72% (58%-84%)</td>
</tr>
<tr>
<td>CE (n = 24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-III vs II-IIIS-V</td>
<td>89% (63%-100%)</td>
<td>69% (44%-81%)</td>
<td>89% (76%-100%)</td>
<td>57% (40%-73%)</td>
<td>73% (54%-88%)</td>
</tr>
<tr>
<td>Non-neoplastic vs nonplastic</td>
<td>88% (23%-100%)</td>
<td>59% (38%-94%)</td>
<td>91% (71%-100%)</td>
<td>59% (40%-78%)</td>
<td>71% (54%-88%)</td>
</tr>
<tr>
<td>NBI (n = 26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-III vs II-IIIS-V</td>
<td>60% (40%-80%)</td>
<td>74% (57%-88%)</td>
<td>89% (86%-92%)</td>
<td>35% (25%-43%)</td>
<td>71% (58%-77%)</td>
</tr>
<tr>
<td>p vs CE</td>
<td>P &lt; .001</td>
<td>P = .315</td>
<td>P &lt; .001</td>
<td>P &lt; .001</td>
<td>73% (58%-81%)</td>
</tr>
<tr>
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<td>76% (48%-100%)</td>
<td>89% (82%-100%)</td>
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<td>73% (58%-81%)</td>
</tr>
</tbody>
</table>

Bisschops et al. Gastrointest Endosc 2017; 86: 1100-1106
Paris Classification

Ulceration: Present

Kudo pit pattern: IIO-IIIL-IV

Borders:
Regular

Histology:
LGD
Paris Classification

Kudo pit pattern: IIIIL

Borders: Regular

Ulceration: Absent

Histology: LGD
New FACILE (Frankfurt Advanced Chromoendoscopic IBD LEsions) classification

<table>
<thead>
<tr>
<th>Endoscopy Findings</th>
<th>SSA/Ps</th>
<th>Inflammatory/Pseudopolyps</th>
<th>Dysplasia LGD/HGD</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphology (mm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Polyoid</td>
<td>Is</td>
<td>Ip</td>
<td>Ila</td>
<td>Ila+IIC</td>
</tr>
<tr>
<td>• Non-Polyoid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Ip, Is, Ila, IIb, IIc, III)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Surface architecture</strong></td>
<td>Roundish</td>
<td>Roundish</td>
<td>Villous Irregular</td>
<td>Irregular/Non structural</td>
</tr>
<tr>
<td>• Roundish</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Villous Regular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Villous irregular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Irregular/Non structural</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vessel architecture</strong></td>
<td>Non visible</td>
<td>Regular</td>
<td>Irregular</td>
<td>Irregular/Non structural</td>
</tr>
<tr>
<td>• Non visible</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Regular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Irregular/Non structural</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inflammation within the lesion</strong></td>
<td>Yes/No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Characterization of the colonic lesion

**Morphology**
Non-Polypoid IIa

**Surface Architecture**
Roundish/villous regular

**Vessels Architecture**
Regular

**Inflammation within the lesion**
No
How do we manage the colonic lesions?

Detection  Characterization  Treatment  Follow-up
ECCO statement 8K
Presence of low grade or high grade dysplasia should be confirmed by an independent gastrointestinal specialist pathologist [EL 5]

ECCO statement 8L
Polypoid dysplasia can be adequately treated by polypectomy provided the lesion can be completely excised, and there is no evidence of non-polypoid or invisible dysplasia elsewhere in the colon [EL2]

ECCO statement 8M
Non-polypoid dysplastic lesions can be treated endoscopically in selected cases. If complete resection can be achieved, with no evidence of non-polypoid or invisible dysplasia elsewhere in the colon, continued surveillance colonoscopy is reasonable [EL 5]. Every other patient with non-polypoid dysplasia should undergo colectomy, regardless of the grade of dysplasia detected on biopsy analysis [EL 2]

ECCO statement 8N
Polyps with dysplasia that arise proximal to segments with macroscopic or histologic involvement are considered as sporadic adenomas and should be treated accordingly [EL 2]

Management of the colonic lesion

“Endoscopically resectable”:

- Margins of the lesion are identified
- The lesion appears to be entirely removed after resection
- Histology confirms the completed removal
- Biopsies taken from adjacent mucosa to the removed lesion are free of dysplasia

Management of the colonic lesion

- The choice in difficult cases should be taken by a multidisciplinary team.

- IBD physician
- GI pathologist
- GI radiologist
- Colorectal surgeon
- IBD interventionist or EMR/ESD specialist

*Shen et al. Gastrointestinal Endoscopy 2018*
Endoscopic resection in IBD

EMR

1. Characterize the lesion

2. Define is it is resectable

Paris Classification

Kudo pit pattern:

Borders: Regular
Ulceration: Absent

Margins identified

Iacucci at al Gut 2018
Endoscopic resection in IBD

**EMR**

3. Submucosal injection

4. Check if the lesion is well-lifted

Iacucci et al Gut 2018
Endoscopic resection in IBD

**EMR**

5. Use a stiff snare to grab the lesion

6. Use hot or cold snared polypectomy
Endoscopic submucosal dissection

Soetikno et al. Gastroenterol Endoscopy 2018; 87: 1085-1094

Iacucci et al Gut 2018
Endoscopic resection in IBD
Treatment of the colonic lesion

If the lesion is not resectable

If there is evidence of dysplasia at the base of the lesion after resection

If endoscopically invisible dysplasia

If multifocal dysplastic lesions

PROCTOCOLECTOMY

ASGE Guidelines, Gastrointestinal Endoscopy 2015; 81:1101-1121
Endoscopic resection in IBD

Follow-up of the colonic lesion

ECCO statement 8M
Non-polypoid dysplastic lesions can be treated endoscopically in selected cases. If complete resection can be achieved, with no evidence of non-polypoid or invisible dysplasia elsewhere in the colon, continued surveillance colonoscopy is reasonable [EL 5]. Every other patient with non-polypoid dysplasia should undergo colectomy, regardless of the grade of dysplasia detected on biopsy analysis [EL 2]


Statement 7: After complete removal of endoscopically resectable polypoid dysplastic lesions, surveillance colonoscopy is recommended rather than colectomy. (100% agreement; strong recommendation; very low quality evidence)

Statement 8: After complete removal of endoscopically resectable nonpolypoid dysplastic lesions, surveillance colonoscopy is suggested rather than colectomy. (80% agreement; conditional recommendation; very low-quality evidence)

Conclusions

- Dye Chromoendoscopy is considered the standard of care to adopt in the daily practice to detect neoplasia in IBD.

- Adopt and implement dye chromoendoscopy technique as standard of practice.

- DCE with targeted biopsies should be preferred to random biopsies, but additional random biopsies may be considered in high risk patients with personal history of neoplasia, concomitant PSC or a ‘tubular’ colon during colonoscopy.
Conclusions

- Novel optical diagnosis virtual chromoendoscopy can better characterize mucosal and vascular pattern and aid the endoscopists to take targeted biopsies.

- New optical enhancement and biopsy diagnosis scopes may help to characterise and assess margins of colonic lesions and plan endoscopic therapeutic strategy.

- Novel advanced endoscopic techniques to personalise in real time targeted endotherapy of the dysplastic lesions.