When and How to use Chromoendoscopy

Samir A. Shah, MD, FACG
Clinical Professor of Medicine, Brown University
Chief of Gastroenterology, The Miriam Hospital
Gastroenterology Associates, Inc
44 West River Street, Providence RI 02904
401-274-4800 samir@brown.edu

Acknowledgements:
Francis Farraye and David Rubin

Learning Objectives

• Understand the increased risk of CRC in IBD
  – Specific risk factors
  – Risk stratify for surveillance
• Recognize limitations of conventional colonoscopy and random biopsy
• Describe the indications for the usage of chromoendoscopy to detect dysplasia in patients with IBD

Take home points

• Increased risk of colon cancer in IBD
  – But, not as high as we used to think
  – Risk stratification

• Polyps in IBD patients: treat like non-IBD
  – Nomenclature: Paris classification, Border, ulcer

• Chromoendoscopy – Yes: increases yield
  May decrease incidence/mortality of CRC

• ASGE Guidelines, SCENIC Consensus

• Confirmed dysplasia = colectomy
  – HGD, endoscopically unresectable dysplasia
  – LGD* controversial

Risk of CRC in IBD is Less Than Previously Reported: Evidence of Successful Prevention?

• 48 studies included in the meta-analysis
• Included both population-based (259,266 person-years at risk) and referral center studies (29,799 patient-years at risk)
• Overall cumulative risk at 10, 20 and >20 years is 1%, 3% and 7%
• Rate higher in referral centers and in patients with extensive disease
• Risk is still almost 2x higher in Crohn’s and ulcerative colitis compared with general population

Cancer Risk Factors in IBD

- Extensive disease
  - No increase in proctitis patients, intermediate risk in left sided UC and highest risk in in pancolitis
- Disease duration/age at diagnosis
- Family history of colorectal cancer
  - Highest risk if FDR with CRC < 50
- Primary sclerosing cholangitis
- Histologic Disease activity
- Previous dysplasia
- Pseudopolyps, strictures, foreshortened colon
- Probable risk factors
  - Poor compliance with medical therapy
  - Male Sex


Cancer Surveillance in Colitis

Inflammation  Dysplasia  Cancer  Death

Initiate screening and surveillance  Intervention to prevent further progression: surgery
Is Surveillance Effective?

• Choi 1993: Patients who underwent surveillance presented with a significantly earlier stage of cancer
  – 5 year survival higher in surveillance group
• Karlen 1998: Relative CRC risk decline with increasing number of colonoscopies
• Eaden 2000: OR for CRC decreased with increasing number of colonoscopies
• Velayos 2006: OR for CRC decreased with increasing number of colonoscopies


Surveillance Colonoscopy in IBD

• Retrospective study of 6823 patients with IBD (2764 with a recent colonoscopy, 4059 without a recent colonoscopy) seen and followed for at least 3 years at 2 tertiary referral hospitals (MGH & BWH) in Boston, Massachusetts
• The incidence of CRC among patients with and without a recent colonoscopy were 1.6% and 2.7% respectively (OR, 0.56; 95%, CI 0.39-0.80)
• Among patients with CRC, a colonoscopy within 6 to 36 months before diagnosis was associated with a reduced mortality rate (OR, 0.34; 95% CI 0.12-0.95)

Conclusion: A recent colonoscopy (within 36 months) is associated with a reduced incidence of CRC in patients with IBD, and lower mortality rates in those diagnosed with CRC

Increased Risk of CRC in IBD

- Study of 55,008 Medicare patients, 15% of IBD patients with a diagnosis of CRC (2001–2005) had undergone surveillance colonoscopy in the previous 3 years
- Compared with non-IBD patients, IBD patients were 3 times more likely (15.5% vs. 5.8%) to have had a colonoscopy within 6 to 36 months before the CRC diagnosis (CD: OR, 3.07; 95% CI, 2.23–4.21; UC: OR, 3.05; 95% CI, 2.44–3.81)
- 62.5% of CD and 38.5% of UC patients with interval CRC had advanced (stage III or IV) CRC at diagnosis

Conclusions: dysplasia may be often missed or unrecognized with standard (old) colonoscopic surveillance techniques


Biopsy Recommendations for Cancer Screening in IBD

<table>
<thead>
<tr>
<th></th>
<th>Dysplasia</th>
<th>Cancer</th>
<th>Dysplasia or Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>90% Confidence</td>
<td>33</td>
<td>34</td>
<td>11</td>
</tr>
<tr>
<td>95% Confidence</td>
<td>56</td>
<td>64</td>
<td>18</td>
</tr>
</tbody>
</table>

- For patients with extensive disease, a minimum of 33 biopsies are recommended
- 4-quadrant biopsies every 10 cm throughout the colon
- Studies done pre HD scopes
- Evidence suggests that recommendations are frequently not observed

- 2000cm² colon SA vs 1.32cm² random SA

33 random biopsies sample <0.1% of the bowel

Random Biopsies Taken During Colonoscopic Surveillance of Patients With Longstanding Ulcerative Colitis: Low Yield and Absence of Clinical Consequences

- 466 surveillance colonoscopies (167 pt)
  - 11,772 biopsies
  - 1 LGD = positive on random biopsies (all others were targeted biopsies)
- Rutter: 1/1266 random bx
- SCENIC:
  - 39/48,522 (0.08%)
  - 10% of dysplasia RB, 90% targeted

van den Broek, Am J Gastroenterol 2011
Rutter MD, J Gastroenterol, 2011:46
Colectomy for Dysplasia in UC

- Low grade dysplasia $\rightarrow$ 20% cancer
- High grade dysplasia $\rightarrow$ 42% cancer
- DALM $\rightarrow$ 43% cancer
- The finding of dysplasia of any grade should be confirmed by a pathologist with special expertise in gastrointestinal pathology
- **Confirmed dysplasia = colectomy**

Bernstein et al, Lancet 1994;334:71

Progression of Neoplasia in UC: Chicago

- 35 patients in analysis
- 2 with IND and 2 with LGD developed HGD or CRC over mean duration of 49.8 months
- Incident rate for advanced neoplasia for all patients was 2.7 cases of HGD or CRC per 100 person-years at risk
- **Conclusion:** a low rate of progression to HGD or CRC in patients with LGD or IND under surveillance
  - Polypoid dysplasia showed less risk of progression than flat dysplasia

IND=indefinite dysplasia

Kaplan-Meier curve of progression to high-grade dysplasia or colorectal cancer in patients with low grade or indefinite dysplasia.

# The Case for Chromoendoscopy

## Chromoendoscopy in Inflammatory Bowel Disease

**Ralf Kiesslich, Markus F. Neurath, MD**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Dye</th>
<th>Staining</th>
<th>Endoscopy</th>
<th>Design</th>
<th>No. of pts.</th>
<th>Pts. with dysplasia</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiesslich et al.</td>
<td>2003</td>
<td>Germany</td>
<td>MB</td>
<td>Pancolonic</td>
<td>Magnification</td>
<td>Randomized 1:1</td>
<td>165</td>
<td>19</td>
<td>32 vs. 10 dysplastic lesions</td>
</tr>
<tr>
<td>Matsumoto et al.</td>
<td>2003</td>
<td>Japan</td>
<td>IC</td>
<td>Pancolonic</td>
<td>WLE</td>
<td>Prospective cohort</td>
<td>57</td>
<td>12</td>
<td>86% vs. 38% sensitivity</td>
</tr>
<tr>
<td>Rutter et al.</td>
<td>2004</td>
<td>UK</td>
<td>IC</td>
<td>Pancolonic</td>
<td>WLE</td>
<td>Prospective cohort</td>
<td>100</td>
<td>7</td>
<td>9 vs. 2 dysplastic lesions</td>
</tr>
<tr>
<td>Hurstone et al.</td>
<td>2005</td>
<td>UK</td>
<td>IC</td>
<td>Targeted</td>
<td>Magnification</td>
<td>Prospective cohort</td>
<td>700</td>
<td>81</td>
<td>69 vs. 24 dysplastic lesions</td>
</tr>
<tr>
<td>Kiesslich et al.</td>
<td>2007</td>
<td>Germany</td>
<td>MB</td>
<td>Pancolonic</td>
<td>CLE</td>
<td>Randomized 1:1</td>
<td>153</td>
<td>15</td>
<td>19 vs. 4 dysplastic lesions</td>
</tr>
<tr>
<td>Marion et al.</td>
<td>2008</td>
<td>US</td>
<td>MB</td>
<td>Pancolonic</td>
<td>WLE</td>
<td>Tandem colonoscopy</td>
<td>102</td>
<td>19</td>
<td>17 vs. 3 patients with dysplastic lesions</td>
</tr>
<tr>
<td>Garth et al.</td>
<td>2011</td>
<td>Germany</td>
<td>IC</td>
<td>Pancolonic</td>
<td>CE</td>
<td>Randomized 1:1:1</td>
<td>150</td>
<td>6</td>
<td>6 (2+ CDH) vs. 0 patients with dysplastic lesions</td>
</tr>
<tr>
<td>Haraty et al.</td>
<td>2011</td>
<td>Slovakia</td>
<td>IC</td>
<td>Pancolonic</td>
<td>CE</td>
<td>Tandem colonoscopy</td>
<td>30</td>
<td>4</td>
<td>4 vs. 2 dysplastic lesions</td>
</tr>
</tbody>
</table>
Chromoendoscopy: Which Dye?

• Indigo carmine (0.03%-0.4%)
  – Contrast stain neither reacts nor is absorbed by the colonic mucosa
  – Pools in mucosal grooves allowing better definition of small or flat lesions as well as alterations in mucosal architecture
  – Can be washed off the mucosa

• Methylene blue (0.04-0.2%)
  – Vital dye taken up by colonic mucosa within 1-2 minutes staining noninflamed mucosa but is poorly taken up by dysplastic tissue or inflamed mucosa

• No published studies comparing indigo carmine to methylene blue in patients with IBD. Other dyes: FD&C#2 Blue

Kiesslich, R et al. Gut 2004;53:165-167

Pit Pattern Classification (Kudo)

The typical crypt architecture of types I-V are indicated (A). (B) Examples of type I (left) and type IV (right) lesions before and after chromoendoscopy.

Kiesslich, R et al. Gut 2004;53:165-167
Chromoendoscopy Videos

Chromoendoscopy: pseudopolyps
Adenoma found in a sea of pseudopolyps

Chromo with IC using flushing device
Chromoendoscopy: pt with longstanding Crohn’s colitis
Polyp seen best with MB

Courtesy: DT Rubin
Can one do chromoendoscopy in a busy clinical practice?

- Time: not an issue (Flusher, targeted biopsies. But schedule for 1 hour)
- Training (15-20 cases); online resources
- Technique: Flusher vs spray catheter
- Does it work in a private practice: yes!
- 2005: started: recorded on op note whether lesion seen with chromo or not
  - Selection bias in patients chosen for Chromo

Chromoendoscopy in practice

- Single physician experience 2005-8/2012
- 184 scopes; 118pts, mean age 51.4 years
  Chromo - IC (64 scopes) WLE (120 scopes)
  38.8 minutes 20.5 minutes
  42.0 bx (13 jars) 34.8 bx (10 jars)
  157 polyps (2.45/scope) 87 polyps (0.725/scope)
  25/64 (39.1%) dys polyps 8/120 (6.9%) dys polyps (p<0.001)

*flat dysplasia on one random biopsy: doing well, no colectomy, annual colonoscopy with chromo since


Is it recommended?

- BSG, ECCO, ESGE, CAG, APAG, JGES: endorse Chromo as preferred!
- CCFA/ASGE/AGA: endorse chromoendoscopy
- SCENIC CONSENSUS STATEMENT
- ACG: not enough data to endorse
  - Ok to do if have expertise, HD scope with random biopsies ok too
  - Though increase in yield of dysplastic lesions, does this translate to less cancer (DoDo Bird analogy- Dr Peter Higgins). Need to show decrease in CRC/mortality

Two non-profit charitable foundations (Maxine and Jack Zarrow Family Foundation and the William Warren Foundation), provided unrestricted gifts supporting the guideline development process
SCENIC Nomenclature

- Dysplasia is either “visible” or “invisible”

SCENIC Nomenclature

- It is recommended that the terms dysplasia-associated lesion or mass (DALM) and adenoma-like or non-adenoma-like DALM be abandoned
- Use the preferred term “endoscopically resectable” which indicates that:
  - distinct margins of the lesion could be identified
  - the lesion appears to be completely removed on visual inspection after endoscopic resection
  - histologic examination of the resected specimen is consistent with complete removal
  - biopsy specimens taken from mucosa immediately adjacent to the resection site are free of dysplasia on histologic examination
- All other lesions are “endoscopically unresectable”


<table>
<thead>
<tr>
<th>Endoscopic appearance</th>
<th>Description**</th>
<th>Definition</th>
<th>Path class***</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polypoid</strong></td>
<td>Pedunculated</td>
<td>Lesion attached to mucosa by a stalk</td>
<td>Ia</td>
</tr>
<tr>
<td></td>
<td>Sessile</td>
<td>Lesion not attached to mucosa by a stalk entire base is contiguous with mucosa</td>
<td>Is</td>
</tr>
<tr>
<td></td>
<td>Slightly elevated</td>
<td>Lesion with protrusion but &lt; 2.5 mm above mucosa</td>
<td>Ila</td>
</tr>
<tr>
<td><strong>Non-polypoid</strong></td>
<td>Flat</td>
<td>Lesion without protrusion above mucosa</td>
<td>Iib</td>
</tr>
<tr>
<td></td>
<td>Depressed</td>
<td>Lesion with at least a portion depressed below the level of mucosa</td>
<td>Iic</td>
</tr>
</tbody>
</table>

ASGE Guidelines

- All patients with UC or Crohn’s colitis are recommended to undergo a screening colonoscopy 8 years after disease onset to (1) re-evaluate extent of disease and (2) initiate surveillance for colorectal neoplasia (Grade: Moderate)

- Surveillance colonoscopy is recommended every 1 to 3 years beginning after 8 years of disease in patients with UC with macroscopic or histologic evidence of inflammation proximal to and including the sigmoid colon and for patients with Crohn’s colitis with greater than one-third of colon involvement (Grade: Moderate)


ASGE: How to Perform Surveillance

- Chromoendoscopy with targeted biopsies is recommended as the preferred surveillance technique to maximize dysplasia detection (Grade: Moderate)

- Chromoendoscopy-targeted biopsies are sufficient for dysplasia surveillance in patients with IBD and that consideration should be given to taking two biopsies from each colon segment for histologic staging to assess extent and severity of inflammation (Grade: Low)

- Random biopsies with targeted biopsies of any suspicious appearing lesions remain a reasonable alternative for dysplasia surveillance if the yield of chromoendoscopy is reduced by significant underlying inflammation, significant pseudopolyposis, or poor preparation or if chromoendoscopy is not available (Grade: Low)

SCENIC: Detection of Dysplasia on Surveillance Colonoscopy

- **High definition** is recommended rather than standard definition colonoscopy *(Strong recommendation)*

- **Chromoendoscopy** is recommended rather than standard-definition white-light colonoscopy *(Strong recommendation)*

- **Chromoendoscopy** is suggested rather than white-light colonoscopy when performing surveillance with high-definition colonoscopy *(Conditional recommendation)*

- **Narrow band is not recommended** as alternative to standard definition or high definition white light endoscopy or chromoendoscopy *(Conditional recommendation)*


<table>
<thead>
<tr>
<th>Purpose</th>
<th>Technique</th>
<th>Method</th>
<th>Dilution*</th>
<th>Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion detection</td>
<td>Pan chromoendoscopy</td>
<td>Water jet channel using auxiliary foot pump or biopsy channel using spray catheter</td>
<td>Indigo carmine (0.8%, 5ml ampule) 2 ampules + 250ml water (0.03%)</td>
<td>Methylene blue (1%, 10ml ampule): 1 ampule + 240ml water (0.04%)</td>
</tr>
<tr>
<td>Lesion characterization and delineation of borders</td>
<td>Targeted chromoendoscopy</td>
<td>Syringe spray through biopsy channel</td>
<td>Indigo carmine (0.8%, 5ml ampule): 1 ampule + 25ml water (0.13%)</td>
<td>Methylene blue (1%, 10ml ampule): 1 ampule + 40ml water (0.2%)</td>
</tr>
</tbody>
</table>

*Various dilutions ranging from 0.03%–0.2% of indigo carmine and methylene blue have been reported for panchromoendoscopy.

What I Do: Chromo for all IBD Surveillance. Targeted biopsies

- In our AEC: 0.1% IC (food coloring grade)
  - Mixed that morning of in 1 liter H₂O.
  - Clean further on way in.
  - Flusher starting in the cecum, panchromoendoscopy by section.
  - Suction pools carefully
  - No significant inflammation. Targeted biopsies only. I book 45 min. (usually takes me 30 min)
- 0.1% MB in hospital (One 10ml vial of MB in 500 cc sterile water)
  - Otherwise same protocol
  - If IC available, Soetikno protocol
  - 1 hour booking in hospital
- Wear scrubs and old sneakers (otherwise your clothes will be stained blue!)

Should You Continue to Obtain Random Biopsies When Using Chromoendoscopy?

- Continue random biopsies in high risk patients such as those with PSC or a previous history of dysplasia
- Use random biopsies as alternative to CE or in patients with poor prep and/or multiple pseudopolyps
- Continue to take several biopsies to document extent and severity of disease
Invisible Dysplasia

If “invisible” dysplasia is detected and confirmed by a second expert pathologist, management must be individualized and is dependent on:

• Low grade dysplasia vs high grade dysplasia
• Unifocal vs multifocal
• Patients risk factors (PSC, duration and extent of disease, FH of CRC, etc)
• Patient preferences


Summary: Management of Dysplasia

• Dysplasia should be confirmed by a second expert pathologist
• Polypoid and nonpolypoid dysplasia can be managed endoscopically if the lesion can be completely resected and there is no adjacent invisible dysplasia; otherwise surgery is required
• Advanced endoscopic techniques may be needed for resection and referral to an experienced endoscopist appropriate
Post SCENIC Studies

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Study Period</th>
<th>Study Design</th>
<th>Cohort</th>
<th>Dysplastic Lesions</th>
<th>Bottom Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choi, UK, 2015</td>
<td>2002-2012</td>
<td>Retrospective</td>
<td>Surveillance</td>
<td>267</td>
<td>CE Superior</td>
</tr>
<tr>
<td>Mooiweer, Dutch, 2015</td>
<td>2000-2013</td>
<td>Retrospective</td>
<td>Surveillance</td>
<td>401</td>
<td>CE no difference</td>
</tr>
<tr>
<td>Marion, US, 2015</td>
<td>2005-2011</td>
<td>Retrospective</td>
<td>Longitudinal</td>
<td>44</td>
<td>CE Superior</td>
</tr>
<tr>
<td>Gasia, Canada, 2016</td>
<td>2011-2013</td>
<td>Retrospective</td>
<td>Surveillance</td>
<td>74</td>
<td>CE no difference</td>
</tr>
<tr>
<td>Deepak, US, 2016</td>
<td>2006-2013</td>
<td>Retrospective</td>
<td>Dysplasia</td>
<td>95</td>
<td>CE Superior</td>
</tr>
<tr>
<td>Parakkal, US, 2016</td>
<td>2006-2013</td>
<td>Retrospective</td>
<td>Dysplasia 95 (78 UC)</td>
<td>40</td>
<td>CE Superior FD&amp;C#2 Blue</td>
</tr>
</tbody>
</table>

Chromoendoscopy superior to Standard in Long Term Surveillance

Marion JF, et al. Clinical Gastroenterology and Hepatology 2016;14:713-719
Ashwin Says “Chromo is Better”

EDITORIAL
Chromoendoscopy Is Better. So Why Am I Not (yet) Using it for Routine Inflammatory Bowel Disease Surveillance?

ASHWIN N. ANANTHAKRISHNAN, MD, MPH
Division of Gastroenterology
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts

Pre-existing risk factors to consider: extent of colonic involvement, years of disease, previous endoscopic and histologic severity of inflammation, FH of CRC at young age (<50), presence of pseudopolyps, previous history of LGD or indefinite for dysplasia, presence of stricture(s), PSC, and male gender.

Post colonoscopy risk factors to consider: Degree and extent of endoscopic/histologic inflammation, presence and extent of pseudopolyps, finding and number of dysplastic polyps completely removed, finding of LGD or indefinite for dysplasia in a random or targeted biopsy, and dysplastic lesion(s) not completely removed.

Colectomy: invasive cancer, unresectable polyoid dysplasia of any grade. Flat HGD found on random biopsy, residual unresectable dysplastic tissue of any grade at follow-up, multifocal HGD on biopsy.

*Isolated LGD can be monitored with close surveillance after discussion of risks, benefits including option of colectomy. Dysplasia of any grade and indefinite for dysplasia should be reviewed by second expert GI pathologist.

- Low Risk: left-sided UC or Crohn’s colitis no other risk factors
  - Begin 8 years after disease
  - If no worrisome findings, repeat in 5 years

- Intermediate Risk: Pseudopolyps and fit of CRC
  - Begin 8 years after disease
  - If no worrisome findings, repeat in 2-3 years

- High Risk: PSC or IBD
  - Begin immediately
  - If no worrisome findings, repeat in 1 year
Stool DNA as Adjunct to Endoscopy

- Pilot studies have demonstrated that methylated DNA markers (BMP3, Vimentin, EYA4, NDRG4) can be detected in stool of IBD patients with dysplasia or CRC
- DNA Chip: N=338, ROC=0.93, Sensitivity 92%, Specificity 94%


Summary

- The absolute risk of CRC in IBD is limited
- Stratify for high risk: Extensive disease, long duration, uncontrolled inflammation, FH of CRC and patients with PSC carry a greater risk of CRC
- To prevent IBD related CRC, the goal is to minimize severity and extent of inflammation, whereas the methods used to do this (regular follow-up, medical treatment, chemoprevention, surveillance, and surgery) act in common and not as single cancer-preventive factors
- Random biopsies have extremely low yield
- Chromoendoscopy detects more dysplasia than HD white light endoscopy
- We need prospective data that chromoendoscopy prevents development of CRC in IBD patients
Why Chromoendoscopy?

• Increases yield of important findings
• No increased risk
• Safe, easy to learn and perform
• Takes more time*: but isn’t your patient worth it? Don’t you take your time on screening colons for high ADR?
• Potential for cost saving (less frequent scopes, no need for random biopsies) Important in the MACRA/MIPS era!
• Should be standard for surveillance in IBD (in my opinion). Negative chromocolonoscopy associated with good long term colectomy free survival
• Long term data needed. Risk stratify with Stool DNA?

*Increased time is negligible if stop random biopsies and use flusher

Have I convinced you to join?