Dysplasia in IBD: Update on Surveillance and Management

David T. Rubin, MD, FACG, FASGE
Joseph B. Kirsner Professor of Medicine
Chief, Section of Gastroenterology, Hepatology and Nutrition

The IBD-Cancer Prevention Formula

- Accurate Risk Identification
  - Which patients?
  - How to quantify risks?

- Accurate Detection of Precancer
  - Understanding of predictive value of lesions
  - Colonoscopy
  - Accurate biopsies
  - Reliable pathology

- Effective Prevention Strategies
  - Pts and MDs implement strategies
  - Colectomy
  - Polypectomy
  - Chemoprevention

= Outcome of interest
  - ↓ Cancer
  - ↓ Mortality
  - ↑ Colectomy
  - ↑ HRQoL
Updated Risk Factors for Dysplasia and Colorectal Cancer in Ulcerative Colitis

**MODIFIABLE (Potentially)**
- Increased inflammatory activity
- Backwash ileitis
- Pseudopolyps
- Prior dysplasia
- Mass/stricture

**IMMUTABLE**
- Male gender
- Longer duration of disease
- Greater extent of colonic involvement
- Family history of CRC
- Primary sclerosing cholangitis
- Younger age of diagnosis

---

Evolution of Cancer Prevention in IBD

<table>
<thead>
<tr>
<th>Modality</th>
<th>Primary Lesion Detected</th>
<th>Outcome</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barium enemas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiberoptics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digital scopes (CCD technology)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD scopes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromoscopy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evolution of Cancer Prevention in IBD

<table>
<thead>
<tr>
<th>Modality</th>
<th>Primary Lesion Detected</th>
<th>Outcome</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination</td>
<td>Metastatic disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barium enemas</td>
<td>Masses, tubular colons</td>
<td>Invasive stage</td>
<td>Prophylactic colectomy</td>
</tr>
<tr>
<td>Fiberoptics</td>
<td>Masses, “DALMs”</td>
<td>Dysplasia thought to be “invisible”</td>
<td>Colectomy</td>
</tr>
<tr>
<td>Digital scopes (CCD technology)</td>
<td>Polypoid/raised lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD scopes</td>
<td>Raised lesions, mucosal defects/abnormal pit patterns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromoscopy</td>
<td>Raised lesions, flat lesions/mucosal defects/abnormal pit patterns</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evolution of Cancer Prevention in IBD

<table>
<thead>
<tr>
<th>Modality</th>
<th>Primary Lesion Detected</th>
<th>Outcome</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination</td>
<td>Metastatic disease</td>
<td>Death</td>
<td>Prophylactic colectomy</td>
</tr>
<tr>
<td>Barium enemas</td>
<td>Masses, tubular colons</td>
<td>Insensitive to early stage lesions; Cancer detected later</td>
<td>Colectomy</td>
</tr>
<tr>
<td>Fiberoptics</td>
<td>Masses, &quot;DALMs&quot;</td>
<td>Dysplasia thought to be &quot;invisible&quot;</td>
<td>Colectomy</td>
</tr>
<tr>
<td>Digital scopes (CCD technology)</td>
<td>Polypoid/raised lesions</td>
<td>Era of random biopsies</td>
<td>Colectomy</td>
</tr>
<tr>
<td>HD scopes</td>
<td>Raised lesions, mucosal defects/abnormal pit patterns</td>
<td>Random/Targeted biopsies</td>
<td>Lesion resection, follow-up with more &quot;intensive&quot; surveillance</td>
</tr>
<tr>
<td>Chromoscopy</td>
<td>Raised lesions, flat lesions/mucosal defects/abnormal pit patterns</td>
<td>Targeted biopsies (fewer?)</td>
<td>Lesion resection, follow-up with more &quot;intensive&quot; surveillance</td>
</tr>
</tbody>
</table>

**Movement away from random biopsies**

**Movement away from surgery**

## Newer Approaches to Dysplasia Management

**Technique**
- Some dysplasia does not require proctocolectomy
- Polypectomy sufficient
- Endoscopic mucosal resection
- Endoscopic Submucosal Dissection
- Subtotal colectomy

**Levels of Evidence**
- Cohort studies of outcomes\(^1,2\)
- Case series\(^3\)
- Case reports
- Anecdotal

---

There is Low Yield of Random Biopsies in Colitis Surveillance

- N=167 patients, 466 surveillance colonoscopies
- 24 of 11,772 random biopsies detected neoplasia (0.2% per-biopsy yield)
- ~1 in 500 random biopsies

Resected “Raised” Dysplasia has Less Risk of Progression than “Flat” Dysplasia

Quality of Pathology and Pathologists

Important!
There is Poor Correlation for Some Grades of Dysplasia

- Adequate biopsy specimens
- Labeled properly
- Communication with your pathologist is key!


K=0.51
Good

K=0.18
Poor

K=0.36
Fair

K=0.54
Good

?  

Expert review of digitized slides

This is Not Your Mentor’s Dysplasia!

- OLD: dysplasia “invisible”
- NEW: technology makes most “visible”
- HYPOTHESIS: Dysplasia found by newer technologies may not have the same meaning as that found in the past
- PROPOSED: This should allow a different approach to detection and follow-up

Changing Terminology: Need for Consistency!

The terms “DALM” and “ALM” are being replaced by:

- “polypoid”
- “non-polypoid”
- “flat”
- “invisible” dysplasia


Approach to Visible Dysplasia in IBD

Dysplasia

Endoscopic appearance

Flat*  Visible by WLE/raised

Grade?

High  Low

Multifocal?

Yes  No

Colectomy  Colectomy vs. aggressive follow-up  Colonoscopy ≤6 months and follow-up

Flat = diagnosed by random biopsy or only visible by chromoendoscopy.

What Is The Utility of Enhanced Visualization?

Chromoendoscopy is Highly Sensitive and Specific for Dysplasia in UC

- Meta-analysis of 6 randomized controlled trials comparing dye-spray to white light/conventional colonoscopy
- Methylene blue or indigo carmine

Polypectomy with Methylene Blue
What Happens to Dysplasia Found on Chromoendoscopy?

- Are we missing occult cancers?
- Dysplasia in the current age has a different predictive value than dysplasia found with earlier technology
- Current therapies prevent progression of dysplasia
- Chromoendoscopy studies:
  - Follow-up in only one study
  - Marion (NYC)
    - Follow-up with colectomy specimens
    - 5 of original 102 had colectomy due to unresectable LGD
    - No CRC


Which Dye Should You Use?

**Methylene Blue**
- Interactions with Serotonergic medications (eg. SSRIs)? 1,2
- Carcinogenic? (DNA damage to colonocytes) 3
- Absorptive, rich dye coloring
- Doesn’t require moving patient around
- Cost comparable to IC
- Shortage (on back order) 5

**Indigo Carmine**
- No known drug interactions
- Not thought to be carcinogenic 3
- Surface dye, less rich staining
- Requires moving patient around to get even distribution of dye
- Cost comparable to MB
- Shortage (was on back order) 6

Challenges to Chromoendoscopy in IBD

- Perception of time consuming and expensive (time plus supplies)
- Unclear if it changes outcomes (cancer or mortality)
- Many patients don’t “qualify” for it due to poor prep or too much inflammation
- No consensus on its use in our field
- No defined training pathway or competency requirement
- Comparison to newer high definition scopes not completed

Billing for Chromoendoscopy

- There is no CPT code for this procedure,¹ nor is there one in the revised Procedural Codes.
- Can try to use -22 modifier (I do)
  - “unusual time, intensity, technical difficult or severity”
  - May pay +10-20% of allowable charge for procedure.
    Reports as well that it may result in decreased reimbursement²
- 43499 and -59 modifier, indicate “chromoendoscopy”²
  - “most time the insurance will deny…”

¹ASGE Technology Committee report, 2007.
Consider Chromoendoscopy for:

- Patients with previous confirmed dysplasia (flat or raised) and high risk and not going to colectomy
- Lesions found and require clarification (selective chromo)
- Patient has minimal inflammation and very good to excellent prep

More Sensitivity to Detect Dysplasia is Not Necessarily Better?

<table>
<thead>
<tr>
<th>DALM seen by White Light (or Barium Enema)</th>
<th>Polypoid dysplasia seen by White Light</th>
<th>Raised lesion identified by direct endoscopy</th>
<th>Flat lesion identified by chromoendoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Sensitivity for Dysplasia</td>
<td></td>
<td></td>
<td>Time</td>
</tr>
<tr>
<td>Specificity for &quot;Clinically Significant&quot; Lesions</td>
<td></td>
<td></td>
<td>Training Direct Costs</td>
</tr>
</tbody>
</table>

SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease

- Rated statements related to surveillance practices based on multiple factors.
- Systematic reviews performed on each topic based on Cochrane methodology.
- Panel voted on recommendations

SCENIC International Consensus Statements
Selected Statements for Consideration

1. When performing surveillance with white-light colonoscopy, high definition is recommended rather than standard definition.

2. When performing surveillance with standard-definition colonoscopy, chromoendoscopy is recommended rather than white-light colonoscopy.

3. When performing surveillance with high-definition colonoscopy, chromoendoscopy is suggested rather than white-light colonoscopy.

4. After complete removal of endoscopically resectable polypoid dysplastic lesions, surveillance colonoscopy is recommended rather than colectomy.

5. After complete removal of endoscopically resectable nonpolypoid dysplastic lesions, surveillance colonoscopy is suggested rather than colectomy.

6. For patients with endoscopically invisible dysplasia (confirmed by a GI pathologist) referral is suggested to an endoscopist with expertise in IBD surveillance using chromoendoscopy with high-definition colonoscopy.
What Do the Guidelines Tell Us?

Table 1. Comparison of Screening Recommendation from International Guidelines for Patients with Crohn's

<table>
<thead>
<tr>
<th>ECCO 2008</th>
<th>ISG 2010 (and NICE)</th>
<th>AGA 2010</th>
<th>ACG 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st screening</td>
<td>Extensive: 2 yearly to 20 yr then annually</td>
<td>10 yr</td>
<td>Max 8 yr</td>
</tr>
<tr>
<td>Surveillance interval</td>
<td>Left-sided: 2 yearly starting at 15 yr</td>
<td>Intermediate 3 yr</td>
<td>1-3 yr</td>
</tr>
<tr>
<td></td>
<td>PSC: 1 yearly</td>
<td>High 1 yr</td>
<td>e.g. PSC</td>
</tr>
<tr>
<td>Chromoendoscopy</td>
<td>Superior to white light endoscopy</td>
<td>Recommended</td>
<td>Special cases</td>
</tr>
<tr>
<td>Biopsies</td>
<td>33+ if no chromo</td>
<td>33+ if no chromo</td>
<td>33+</td>
</tr>
</tbody>
</table>

Because the sensitivity for detecting dysplasia by chromoendoscopy is higher than that of white light endoscopy, chromoendoscopy with targeted biopsies is recommended as an alternative to random biopsies for endoscopists who have expertise with this technique.

-AGA Technical Review 2010

British Society Guidelines 2010

Screening colonoscopy at 10 years (preferably in remission, pancolonic dye-spray)

- Lower Risk
  - Extensive colitis with NO ACTIVE endoscopic/histological information
  - OR left-sided colitis
  - OR Crohn's colitis of <50% colon

- Intermediate Risk
  - Extensive colitis with MILD ACTIVE endoscopic/histological information
  - OR post-inflammatory polyps
  - OR family history CRC in FDR aged 50+

- Higher Risk
  - Extensive colitis with MODERATE/SEVERE ACTIVE endoscopic/histological inflammation
  - OR stricture in past 5 years
  - OR dysplasia in past 5 years declining surgery
  - OR PSC / transplant for PSC
  - OR family history CRC in FDR aged <50

FDR, first-degree relative; PSC, primary sclerosing cholangitis

British Society Guidelines 2010

Screening colonoscopy at 10 years (preferably in remission, pancolonic dye-spray)

**Lower Risk**
- Extensive colitis with NO ACTIVE endoscopic/histological inflammation
- OR left-sided colitis
- OR Crohn's colitis of <50% colon

5 Years

**Intermediate Risk**
- Extensive colitis with MILD ACTIVE endoscopic/histological inflammation
- OR post-inflammatory polyps
- OR family history CRC in FDR aged >50

3 Years

**Higher Risk**
- Extensive colitis with MODERATE/SEVERE ACTIVE endoscopic/histological inflammation
- OR stricture in past 5 years
- OR dysplasia in past 5 years declining surgery
- OR PSC / transplant for PSC
- OR family history CRC in FDR aged <50

1 Year

Other Considerations
- Patient preference, multiple post-inflammatory polyps, age and comorbidity, accuracy and completeness of examination

FDR, first-degree relative; PSC, primary sclerosing cholangitis
What We Still Need!

- Updated guidelines
- Clarification of quality measures
  - Prep
  - Detection rates
- Uniformity of endoscopy reports
- Improved techniques

Future Techniques

- Fecal DNA
  - Stool assays of methylated genes (such as vimentin, EYA4, BMP3, NDRG4) may detect colorectal neoplasms\(^1\)

- Other Markers (mucosal antigens, genetics)

- Confocal Laser Endomicroscopy\(^2\)

---


Why It’s Time to Enter a NEW Era of Surveillance and Cancer Prevention in IBD

- Evidence for guidelines is weak or moderate at best
- Clinicians don’t follow existing guidelines
- We can stratify based on individual risk factors for neoplasia
  - Includes inflammation
- We can learn and apply new techniques

Risk Stratification of Dysplasia in Colitis Guide

Follow-up and Colectomy Recommendations

**Pt/disease-related factors:**
- PSC
- Family history of CRC
- Duration
- Degree of inflammation over time and on last exam
- Male vs Female
- Willingness and ability to follow your recommendations

**Dysplasia-related factors:**
- **Grade:**
  - IND vs. LGD vs. HGD
- **Morphology**
  - Flat vs. Polypoid
  - "Invisible" vs. raised
- **Field effect/Synchronicity:**
  - Unifocal vs. multifocal
- **Longitudinal follow-up?**
  - Dysplasia on a single exam vs. metachronous lesions on serial exams
Summary: Dysplasia in IBD: Update on Surveillance and Management

- Evolving optical technology has made identification of dysplasia easier.
- Random biopsies for surveillance are of limited utility.
- Not all dysplasia requires immediate colectomy.
- Stratify your UC (and Crohn’s colitis) patients by individual risk factors.
- Consider chromoendoscopy (with methylene blue or indigo carmine)
  - when you have been trained
  - in higher risk patients
  - previous confirmed dysplasia (flat or raised)
  - lesions found and require clarification
- Don’t hesitate to get a second opinion (from IBD endoscopist or surgeon).