Clinical Pearls in the Evaluation and Management of Dysplasia

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Co-Director Inflammatory Bowel Disease Center
University of Chicago, Chicago, IL

Major Advances in CRC Prevention in IBD

• Cancer is less prevalent than previously described.
• Inflammation is a confirmed risk factor.
• Random biopsies are of very low yield.
• Chromoscopy is superior to white light for dysplasia detection.
• 5-ASA may not be chemoprotective; Thiopurines may be (?)
• Risk stratification for follow-up is a reasonable approach.
**CRC risk in IBD**

- 9 recent population-based studies
- 323,536 person-years
- Standardized Incidence Ratio (SIR) is equal for CD, UC and IBD combined (1.7; 95% CI, 1.3-2.1)

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**Cumulative Risk in IBD Patients**

- Overall
- Population Based
- Referral Center

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**Cancer**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Cause (Infection/Inflammation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric cancer</td>
<td>Chronic superficial gastritis</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>Chronic HPV or HCV infection</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>HPV infection</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>Sclerosing cholangitis, other inflammation of biliary tract</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>Sporadic, hereditary forms of chronic pancreatitis</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>KS herpes virus (HHV 8)</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>Helicobacter pylori infection</td>
</tr>
<tr>
<td>Gallbladder cancer</td>
<td>Chronic salmonella infection</td>
</tr>
<tr>
<td>Hepatocellular cancer</td>
<td>Chronic hepatitis C</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Pulmonary chronic inflammation:</td>
</tr>
<tr>
<td></td>
<td>- Adult asthma, tuberculosis, postinflammatory interstitial fibrosis (silicosis, asbestosis)</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Ulcerative colitis and Crohn’s colitis</td>
</tr>
</tbody>
</table>
Risks of Dysplasia or CRC in IBD

- Longer duration of disease
- Greater extent of colonic involvement
- Increased inflammatory activity
- Family history of CRC
- Primary sclerosing cholangitis
- Younger age of diagnosis
- Backwash ileitis
- Mass/stricture
- Prior dysplasia
- Pseudopolyps
- Male gender


The IBD-Cancer Prevention Formula

Accurate Risk Identification + Accurate Detection of Precancer + Effective Prevention Strategies = Outcome of interest

- Which patients?
- How to quantify risks?
- Understanding of predictive value of lesions
- Colonoscopy
- Accurate biopsies
- Reliable pathology
- Pts and MDs implement strategies
- Colectomy
- Polypectomy
- Chemoprevention
- ↓ Cancer
- ↓ Mortality
- ↓ Colectomy
- ↑ HRQoL
### Evolution of Cancer Prevention in IBD

<table>
<thead>
<tr>
<th>Modality</th>
<th>Colonic Preparation</th>
<th>Primary Lesions</th>
<th>Outcome</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical examination</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barium enemas</td>
<td>Cathartic prep</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiberoptics</td>
<td>Cathartic prep</td>
<td></td>
<td></td>
<td>Effective chemoprevention</td>
</tr>
<tr>
<td>Digital scopes (CCD technology)</td>
<td>Cathartic prep White light</td>
<td></td>
<td></td>
<td>Cure of colitis</td>
</tr>
<tr>
<td>HD scopes</td>
<td>Cathartic prep White light OR narrow band imaging or mucosal dye spray</td>
<td></td>
<td></td>
<td>None</td>
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**PROGRESS**

- Effective chemoprevention
- Cure of colitis
### Evolution of Cancer Prevention in IBD

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<tbody>
<tr>
<td>Physical examination</td>
<td>None</td>
<td>Metastatic disease</td>
<td>Death</td>
<td>Prophylactic colectomy</td>
</tr>
<tr>
<td>Barium enemas</td>
<td>Cathartic prep</td>
<td>Masses, tubular colons</td>
<td>Inensitive to early stage lesions; Cancer detected later</td>
<td>Colectomy</td>
</tr>
<tr>
<td>Fiberoptics</td>
<td>Cathartic prep White light</td>
<td>Masses, “DALMs”</td>
<td>Dysplasia thought to be “invisible”</td>
<td>Colectomy</td>
</tr>
<tr>
<td>Digital scopes (CCD technology)</td>
<td>Cathartic prep White light</td>
<td>Polypoid/raised lesions</td>
<td>Era of random biopsies</td>
<td>Colectomy</td>
</tr>
<tr>
<td>HD scopes</td>
<td>Cathartic prep White light OR narrow band imaging or mucosal dye spray</td>
<td>Raised lesions, mucosal defects/abnormal pit patterns</td>
<td>Targeted biopsies</td>
<td>Lesion resection, follow-up with more “intensive” surveillance</td>
</tr>
<tr>
<td>Effective chemoprevention</td>
<td>Not needed</td>
<td>Prevention of primary lesions</td>
<td>No neoplasia</td>
<td>Fewer colonoscopies</td>
</tr>
<tr>
<td>Cure of colitis</td>
<td>None</td>
<td>None</td>
<td>No neoplasia</td>
<td>Not needed</td>
</tr>
</tbody>
</table>

**ACG Surveillance Guidelines UC 2010**

(Secondary Prevention)

- **Who**: left-sided or pan-UC more than 8-10 years (exception: PSC and UC- start immediately)
- **Technique**: random biopsies every 10 cm of mucosa; at least 33 biopsies; extra focus on nodules, masses, strictures
- **How often**: q 6 months-2 years
- **Outcome (reviewed by second pathologist)**:
  - High-grade dysplasia: colectomy
  - Low-grade dysplasia: consider colectomy
  - Indefinite dysplasia: increase surveillance?
  - Atypia or indeterminate: treatment of active disease, repeat colonoscopy and biopsies

Guidelines for Surveillance in CD

AGA Position statement

- Crohn’s colitis (not isolated ileitis)
- At least one-third of the colon
- ≥8 years of disease
- Similar approach to UC

Problems with the Current U.S. Surveillance Guidelines

- No prospective evidence of mortality benefit (or even CRC benefit)
- Low rates of observer agreement in histopathologic interpretation
- No risk stratification based on multiple variables (e.g. inflammation and PSC, etc.)
- No adjustment for improved technology or understanding of natural history
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


How sure are you about this dysplasia?
Confidence varies with grade.

<table>
<thead>
<tr>
<th>Dysplasia Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>K=0.51</td>
</tr>
<tr>
<td>K=0.18</td>
</tr>
<tr>
<td>K=0.36</td>
</tr>
<tr>
<td>K=0.54</td>
</tr>
<tr>
<td>No dys</td>
</tr>
<tr>
<td>Good</td>
</tr>
</tbody>
</table>

K=0.51
Good

K=0.18
Poor

K=0.36
Fair

K=0.54
Good

?  

*Expert review of digitized slides*

Dysplasia is Often Not “Invisible”!

• “Invisible”: indistinguishable from surrounding inflamed or quiescent mucosa
• “Visible”
  – Polypoid “adenoma-like” lesion
  – Irregular borders “spreading” lesion, not endoscopically resectable (DALM)
  – Mass
  – Stricture
• Optical colonoscopy sensitivity (retrospective studies\(^1\),\(^2\)):
  – Per lesion sensitivity: 61.6%-77.3%
  – Per patient sensitivity: 78.3%-89.3%

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


What is the utility of enhanced visualization?
### Chromoendoscopy Finds More Dysplasia than Conventional Exams

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Institution</th>
<th># of UC Patients</th>
<th>Type of Imaging</th>
<th>Number of Dysplastic Lesions</th>
<th>Sensitivity / Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiesslich (2003)</td>
<td>University of Mainz, Germany</td>
<td>263</td>
<td>Methylene blue</td>
<td>32</td>
<td>10</td>
</tr>
<tr>
<td>Rutter (2004)</td>
<td>St. Mark’s Hospital, Harrow, UK</td>
<td>100</td>
<td>Indigo carmine</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Hultstone (2005)</td>
<td>The Royal Hallamshire Hospital, Sheffield, UK</td>
<td>350</td>
<td>Indigo Carmine-and Magnification</td>
<td>69</td>
<td>24</td>
</tr>
<tr>
<td>Kiesslich (2007)</td>
<td>University of Mainz, Germany</td>
<td>161</td>
<td>Confocal endomicroscopy</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Dekker (2007)</td>
<td>Academic Medical Center, Amsterdam, The Netherlands</td>
<td>42</td>
<td>Narrow-band imaging</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Marion (2008)</td>
<td>Mount Sinai, New York, USA</td>
<td>102</td>
<td>Methylene Blue</td>
<td>17</td>
<td>9</td>
</tr>
</tbody>
</table>
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


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, active inflammation
- There has not been consensus on its use in our field (yet)
- There is not a defined training pathway or competence requirement
My Approach to Chromoendoscopy

- **WHO:**
  - Pancolonic: High risk (PSC, previous confirmed dysplasia)
  - Segmental: Lesions found and require clarification
- **PREP:** needs to be CLEAN and in remission
- **TYPE:** Methylene blue diluted (my preference)
- **HOW:**
- **FOLLOW-UP:** Depends...

“SURFACE” guidelines for chromoendoscopy

- **Strict** patient selection
  - Avoid active disease
- **Unmask** the mucosal surface
  - Excellent bowel prep; remove mucus and debris
- **Reduce** peristaltic waves
- **Full-staining** length of the colon
- **Augmented** detection with dyes
  - 0.4% indigo carmine; 0.1% methylene blue
- **Crypt** architecture analysis
  - Pit pattern III/IV of concern
- **Endoscopic** targeted biopsies
  - Biopsy all mucosal alterations, especially pit pattern III/IV
Pit Patterns with Chromoendoscopy

Kudo S et al. Endoscopy 1993
Narrow Band Imaging is not Superior to Conventional Colonoscopy for Dysplasia Detection in UC

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>NBI</th>
<th>WLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dekker et al. (2007)</td>
<td>Tandem</td>
<td>42</td>
<td>8/11^a (73%)</td>
<td>7/11^a (64%)</td>
</tr>
<tr>
<td>Van den Broek et al. (2011)</td>
<td>Tandem</td>
<td>48</td>
<td>8/11^a (73%)</td>
<td>9/11^a (82%)</td>
</tr>
<tr>
<td>Ignjatovic et al. (2012)</td>
<td>Parallel group</td>
<td>112</td>
<td>5/56^b (9%)</td>
<td>5/56^b (9%)</td>
</tr>
</tbody>
</table>

NBI: Narrow band imaging; WLE: White light endoscopy.

^aProportion of total dysplastic lesions detected overall; ^bProportion of patients with at least one dysplastic lesion.


More Sensitivity to Detect Dysplasia is Not Necessarily Better?

DALM seen by White Light (or Barium Enema)
Polypoid dysplasia seen by White Light
Raised lesion identified by chromoendoscopy
Flat lesion identified by chromoendoscopy
What Do the Guidelines Tell Us?

<table>
<thead>
<tr>
<th>Table 1. Comparison of Screening Recommendation from International Guidelines for Patients with Celitis.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECG 2008</strong></td>
</tr>
<tr>
<td>1st screening</td>
</tr>
<tr>
<td>Surveillance interval</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Chromoendoscopy</td>
</tr>
<tr>
<td>Biopsies</td>
</tr>
</tbody>
</table>

ECCO: European Crohn’s and Colitis Organization; BSG, British Society of Gastroenterology; NICE, National Institute for Clinical Excellence; AGA, American Gastroenterological Association; ACG, American College of Gastroenterology; PSC, primary sclerosing cholangitis.


Billing for Chromoendoscopy

- “There is no CPT code for this procedure”\(^1\)
- -22 modifier
  - “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 reimbursement\(^2\)
- 43499 and -59 modifier, indicate “chromoendoscopy”\(^2\)
  - “most time the insurance will deny…”

\(^1\)ASGE Technology Committee report, 2007.
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

Intermediate Risk
- Extensive colitis with MILD ACTIVE endoscopic/histological inflammation
- 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

Quality Metrics in Endoscopy: How shall we translate for IBD?

- Quality metrics represent quality in endoscopy pertinent to pre-, intra-, and post-procedural periods.
- Quality metrics designed for different endoscopic procedures.
- Are most studied and best validated in colonoscopy.
- Main goals in colonoscopy:
  - To consistently reach the cecum in most cases (at least 90-95%).
  - To identify all lesions in particular.
  - To remove them safely.
Future (less invasive) Techniques

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

• Other Markers (mucosal antigens, genetics)

### Relationship between AZA and 6MP and CRC

<table>
<thead>
<tr>
<th>Study</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutter 2004</td>
<td>0.3</td>
<td>0.2-0.9</td>
</tr>
<tr>
<td>Croog 2005</td>
<td>0.9</td>
<td>0.5-1.8</td>
</tr>
<tr>
<td>Velayos 2006</td>
<td>3.0</td>
<td>0.7-13.6</td>
</tr>
<tr>
<td>Rubin 2006</td>
<td>0.3</td>
<td>0.1-0.7</td>
</tr>
<tr>
<td>Beaugerie L 2008</td>
<td>0.3</td>
<td>0.1-0.9</td>
</tr>
</tbody>
</table>

*Rutter M et al. Gastroenterology 2004; 126:451*


Velayos F et al. *Gastroenterology* 2006; 130:1941

Rubin D et al. DDW 2006

### Explanation for Observed Differences in Human Chemoprevention Trials

- Inadequate duration of follow-up or limited long-term data on drug use
- Limit accounting for confounding variables
  - Adherence to therapy (all studies)
  - Follow-up/selection bias (all studies)
  - Degree of inflammation
  - Family history of CRC (population studies)
  - Extent/duration of disease (population studies)
- Pharmacy/patient reported data limited in duration and accuracy
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study Type</th>
<th># of patients</th>
<th>Dysplasia or Cancer</th>
<th># of exposures (5-ASA or sulfa)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutter et al. (2004)</td>
<td>Nested case-control study (referral)</td>
<td>68 UC/CRC, 136 UC controls</td>
<td>68</td>
<td>(5-ASA) &lt;3 mo &gt;20 yrs</td>
<td>2.1 (0.6-6.9)</td>
</tr>
<tr>
<td>Rubin et al. (2006)</td>
<td>Case-control study (referral)</td>
<td>59 UC/neoplasia, 141 UC controls</td>
<td>59</td>
<td>1.2 vs. &lt;1.2 g daily</td>
<td>0.75 (0.35-1.63)</td>
</tr>
<tr>
<td>Siegel &amp; Sands (2006)</td>
<td>Case-control study</td>
<td>27 CD/CRC, 27 CD controls</td>
<td>27</td>
<td>(5-ASA) regular use</td>
<td>0.3 (0.05-1.17)</td>
</tr>
<tr>
<td>Ullman et al. (2004)</td>
<td>Cohort study (referral)</td>
<td>314 UC patients without neoplasia at surveillance</td>
<td>43</td>
<td>(5-ASA) &gt;2 g qd &lt;2 g qd</td>
<td>0.9 (0.5-1.8)</td>
</tr>
<tr>
<td>Strevel et al. (2005)</td>
<td>Case-control study</td>
<td>1351 CD, 65 matched cancer patients</td>
<td>65</td>
<td>(5-ASA) Azathioprine (5-ASA)</td>
<td>Reduced Cancer No effect</td>
</tr>
<tr>
<td>Smith et al. (2005)</td>
<td>Cohort study (referral)</td>
<td>24 PSC and IBD</td>
<td>9</td>
<td>(5-ASA) Any vs no mesalamine</td>
<td>0.5 (0.2-1.6)</td>
</tr>
</tbody>
</table>

### Additional NEGATIVE Studies of 5-ASA Chemoprevention

**Stratifying Dysplasia in Order to Make Decisions**

- **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
Stratifying Dysplasia in Order to Make Decisions

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Summary: Clinical Pearls in the Evaluation and Management of Dysplasia

- Stratify risk of neoplasia in your IBD patients- individualize your approaches
- Evolving optical technology has made identification of dysplasia easier.
- Random biopsies for surveillance are of limited utility.
- Surveillance colonoscopy is still necessary for both UC as well as CD.
- Chromoendoscopy is superior to white light examinations, but limitations remain to its widespread incorporation.
- Consider chromoendoscopy:
  - when you have been trained
  - in high risk patients
  - when the patient’s inflammation is controlled and the prep is excellent
  - previous confirmed dysplasia (flat or raised)
  - lesions found and require clarification
  - minimal inflammation.

- Dysplasia found in areas of colitis (by any method) should prompt careful follow-up, escalation of risk category, and surgical consultation.