Updated Risk Factors for Dysplasia and Colorectal Cancer in Ulcerative Colitis

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

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

St. Mark’s 40 Year Surveillance Data (UK)

Incidence Rate of CRC over 40 Years

Shift to Earlier Stage Cancers

Multinational Data on Colorectal Cancer Incidence in IBD

Rate of CRC in UC

Rate of CRC in CD


Why is UC-CRC Incidence Rate Decreasing?

- Secondary prevention is more effective:
  - Surveillance colonoscopies identify lesions that can be resected or result in surgery
- Primary prevention is effective:
  - Medical therapy controls inflammation, reduces risk

Therefore, the message currently is to manage the disease and perform surveillance as effectively as possible!

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>Fiber optics</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>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 “intensive” 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 “intensive” surveillance</td>
</tr>
</tbody>
</table>

Movement away from random biopsies
Movement away from surgery
Movement Away From The Random Biopsy Paradigm

- Estimated that at least 33 biopsies must be obtained to achieve 90% confidence that sampled mucosa would yield dysplasia if present\(^1\)
- 54% of 300 gastroenterologists surveyed took less than the number of recommended biopsies\(^2\)
- ~1 in 500 random biopsies yields dysplasia\(^3\)
  - N=167 patients, 466 surveillance colonoscopies
  - 24 of 11,772 random biopsies detected neoplasia (0.2% per-biopsy yield)

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\(^1\)Naymagon S, Marion JF. Gastrointest Endosc Clin N Am. 2013;23(3):679-94.

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Increase resolution for detecting neoplastic lesions

- **SD White Light (WL)**
  - 640 x 480 pixels
  - 62% sensitivity
  - 78% specificity

- **HD White Light (WL)**
  - 93% sensitivity
  - 85% specificity

- **SD WL + NBI**
  - 61% sensitivity
  - 78% specificity

- **SD WL + Dye Spray**
  - 75% sensitivity
  - 81% specificity

- **HD WL + NBI**
  - 87% Sensitivity
  - 90% Specificity

- **HD WL + Dye Spray**
  - 91% Sensitivity
  - 89% Specificity

Iacucci M. ECCO 2016 (Poster Presentation), Amsterdam, Netherlands.
Narrow Band Imaging

- Comparisons between NBI and dye spray chromoendoscopy have been mixed.
- No difference in dysplasia yield between NBI and HDWLE
- Lower false negative biopsy rates and shorter procedure times\(^1\)

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Outcome</th>
<th>Metric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ignjatovic et al(^2)</td>
<td>112</td>
<td>No significant difference between NBI and HD WLE</td>
<td>9% yield in both treatments</td>
</tr>
<tr>
<td>van den Broek et al(^3)</td>
<td>48</td>
<td>No significant difference between NBI and HD WLE</td>
<td>82% of patients diagnosed with HD vs 73% by NBI</td>
</tr>
<tr>
<td>Pellisé et al(^4)</td>
<td>60</td>
<td>Higher patient miss rate with NBI but comparable true positive rate</td>
<td>46.2% patients incorrectly diagnosed with NBI vs 15.4% with CE</td>
</tr>
</tbody>
</table>


Chromoendoscopy is Highly Sensitive and Specific for Dysplasia in UC

- Meta-analysis of randomized controlled trials comparing incremental yield of dysplasia detection between chromoendoscopy (CE) and white light endoscopy (WLE)
- Methylene blue or indigo carmine

High Definition Colonoscopy in IBD

- **HD > SD colonoscopy**
  - Improves detection of dysplasia

- **HD Chromo > HD white light**
  - More dysplasia detected per patient than HD WLE
    - 6 lesions in 5 patients (WLE) vs. 14 lesions in 11 patients (CE)
  - Greater proportion of flat lesions visualized compared to HD WLE
    - N=95; CE after WLE identified 40 new lesions in 30 patients.

- **HD white light does not miss cancer in patients with LGD**

- **Surveillance biopsies surrounding dysplastic lesions show low rates of dysplasia and no predictive value**

Use of Chromoendoscopy in IBD Surveillance Does Not Increase Dysplasia Detection Over HDWLE

- **CE**: 440 colonoscopies in 401 patients;
- **CE**: 10% (dysplasia detected in 48/440 colonoscopies), 95% CI 6–14%
- **WLE**: 11% (dysplasia detected in 189/1802 colonoscopies), 95% CI 9–13%
- Neoplasia detection rate remains similar between CE and WLE with random biopsies over time
## Chromoendoscopy After White Light Colonoscopy for Dysplasia

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Type</th>
<th>N</th>
<th>Lesions found</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deepak P</td>
<td>2016</td>
<td>retrospective</td>
<td>95</td>
<td>Index WLE: 72</td>
<td>CE in patients with a history of dysplasia on WLE frequently identifies new lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>First CE: 69 (34 new)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Second CE: 34 (26 new)</td>
<td></td>
</tr>
<tr>
<td>Rubin DT</td>
<td>2016</td>
<td>retrospective</td>
<td>37</td>
<td>26/62 lesions</td>
<td>Additional synchronous lesions found</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>28 additional on follow-up</td>
<td></td>
</tr>
</tbody>
</table>


## Follow Up of Dysplasia Found by Chromoendoscopy

- Follow-up with colectomy specimens
- 10 of original 102 had colectomy due to unresectable LGD
- No CRC

If Not Everyone, Who Should Have Chromoendoscopy?

- 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
- PSC?


What Should You Do When Dysplasia is Found?

<table>
<thead>
<tr>
<th>Technique</th>
<th>Levels of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Some dysplasia does not require proctocolectomy</td>
<td>Cohort studies of outcomes¹,²</td>
</tr>
<tr>
<td>Polypectomy sufficient</td>
<td>Case series³,4,5</td>
</tr>
<tr>
<td>Endoscopic mucosal resection</td>
<td>Case reports⁶</td>
</tr>
<tr>
<td>Endoscopic submucosal dissection</td>
<td>Anecdotal</td>
</tr>
<tr>
<td>Subtotal colectomy</td>
<td></td>
</tr>
</tbody>
</table>

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 v 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

Upcoming Technologies
Cellvizio® (Mauna Kea Technologies Inc. Suwanee, GA)

- In vivo histology now possible
- High interobserver agreement and more sensitive than white light endoscopy for detecting neoplasia
- Reveals inflammation where white light endoscopy exhibits uninflamed mucosa
- Correlated with dysplasia found by histopathology
- CE guided laser endomicroscopy has a higher sensitivity and specificity than chromoendoscopy alone.

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CE-Guided PCLE</td>
<td>100% (99-100)</td>
<td>85.7% (57.2-98.2)</td>
<td>77.8% (40.0-97.2)</td>
<td>100 (73.5-100)</td>
</tr>
<tr>
<td>CE Alone</td>
<td>85.7% (42.1-99.6)</td>
<td>64.3% (35.1-87.2)</td>
<td>54.5% (23.4-83.1)</td>
<td>90.0 (55.5-99.7)</td>
</tr>
</tbody>
</table>

1Buchner AM. DDW 2016; San Diego, CA. (Poster Presentation).

FICE (Flexible Spectral Imaging Color Enhancement/Fuji Intelligent Chromo Endoscopy)
Fujifilm Medical Co, Tokyo, Japan

- Another tool with similar utility to chromoendoscopy
  - Displays image in one of 10 preset wavelengths in real time
  - Improved ability to assess structural and vascular patterns on the surface of polyps over white light
- Similar imaging modalities, such as iScan (Pentax Medical, Japan) are able to detect early signs of mucosal healing
- Improves accuracy of in-vivo diagnosis of adenoma: 86% vs. 75%
- Chromoendoscopy superior to FICE alone

David T. Rubin, MD, FACG

Dye Spray Vs Virtual Chromoendoscopy (iSCAN)

- 75 patients assessed 1:1:1
  - HD, Dye Spray, Virtual Chromoendoscopy
- HD had a sensitivity of 93.6%, specificity of 85%
- DCE did not show higher detection of neoplastic lesions than HD

<table>
<thead>
<tr>
<th>Lesions</th>
<th>HD</th>
<th>DCE</th>
<th>VCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSA</td>
<td>13</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Tubular Adenoma</td>
<td>24</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Dysplasia Polypoid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LGD</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>HGD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dysplasia Non Polypoid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LGD</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>HGD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adeno-carcinoma</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>23</td>
<td>22</td>
</tr>
</tbody>
</table>

Molecular Beacons

- Visualization of cells in-vivo through the use of molecular probes
- Utility for flat lesions?
  - Current trials show 81% and 82% sensitivity and specificity for detection of neoplastic lesions
  - Fluorescence imaging may still carry the risk of missing lesions that do not have targeted biomarker


Assistive Technologies

• Computer aided diagnostic systems have approached upwards of 93% accuracy in diagnosing histology of lesions.
• Operator experience independent
• Creates dictionaries of features to compare a region of interest against

Summary: Detection and Management of Dysplasia in IBD

• High definition white light is superior in detecting neoplasia when compared to standard definition
• Dye spray chromoendoscopy surpasses SD white light endoscopy in neoplasia detection, including flat lesions
• Narrow band imaging cannot yet be recommended as an alternative to chromoendoscopy in IBD
• HD WL may be equally good to chromoendoscopy
• New imaging technologies on the horizon may allow for experience independent decision making