What is New in IBD-Related Colorectal Cancer?

- Longer studies of risk and natural history have been completed
- Incidence appears to have decreased over the years
- Risk factors have been clarified to allow for stratification of patient types
- Imaging technologies have improved
- Movement away from total proctocolectomy
Ongoing Questions About Screening/Surveillance

• Who is at risk?
• What technique should we use?
  – What is the optimal method of detecting dysplasia?
  – Random or targeted biopsies?
  – When should chromoendoscopy be performed?
• When is active surveillance appropriate instead of surgery?
Cumulative Risk of Developing CRC in UC
Historical Meta-Meta-Analysis

Cumulative Probability (%)

Time From Diagnosis (y)

Cumulative Probability (%)

CL=confidence limit


The Risk of Colorectal Cancer in Inflammatory Bowel Disease is Declining

Meta-analysis that included 9 population-based studies

323,536 person-years

Standardized Incidence Ratio equal for CD, UC and IBD combined

1.7 (95% CI, 1.3-2.1)

Updated Risk Factors for IBD-Related CRC

Patient-Related Factors:
- Longer duration
- Greater extent of disease
- PSC
- Family history of CRC
- Increased degree of inflammation
- Being male

Dysplasia-Related Factors:
- Grade:
  - HGD > LGD
- Morphology:
  - Flat lesions vs. polypoid
  - “Invisible” vs. raised
- Field Effect:
  - Multifocal vs. unifocal

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

Incidence Rate of CRC over 40 Years

Shift to Earlier Stage Cancers

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 should be to manage the disease and perform surveillance as effectively as possible!

But what is that?

Case 1:

• 35 year old woman with panulcerative colitis since age 27.
• Stable remission on mesalamine, once daily.
• Last “flare” 3 years ago, treated with short course of steroids.
• PMH: none, no PSC
• FH: no IBD, no CRC

• Returns to clinic for routine follow-up.
Ongoing Questions About Screening/Surveillance

• Why do we do it?
• What technique should we use?
  – What is the optimal method of detecting dysplasia?
  – Random or targeted biopsies?
  – When should chromoendoscopy be performed?
• When is active surveillance appropriate instead of surgery?

What Do the Guidelines Tell Us?

| Table 1. Comparison of Screening Recommendation from International Guidelines for Patients with Colitis |
|-------------------------------------------------|--|---|--|---|
| ECCO 2008 | BS 2010 (and NICE) | AGA 2010 | AGA 2019 |
| 1st screening | 8-10 yr | 10 yr | Max 8 yr | 8-10 yr |
| Surveillance interval | Extensive: 2 yearly to 20 yr then annually | Low risk: 5yr | Max 8 yr | 1-3 yr |
| | Left sided: 2 yearly starting at 15 yr | Intermediate 5yr | More often at high risk | 1-2 yr |
| | PSC: 1 yearly | High 1yr | e.g., PSC | |
| Chromoendoscopy | Superior to white light endoscopy | Recommended | Special cases | Not yet |
| Biopsies | 3+ if no chromo | 3+ if no chromo | 3+ if no chromo | |

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

**Surveillance for Colorectal Endoscopic Neoplasia detection and management in Inflammatory bowel disease patients: International Consensus (March 7-8, 2014).**

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

**Dysplasia detection**

- Retrospective study, 369 surveillance colonoscopies
  - 160 standard definition and 209 high definition
- Dysplasia was detected in twice as many patients using HD scopes
  (adjusted prevalence ratio=2.2)

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**Statement 1:** When performing surveillance with white-light colonoscopy, high definition is recommended rather than standard definition. (80% agreement; strong recommendation; low-quality evidence)

SCENIC Consensus Statement. Gastrointest Endosc, 2015

Case 1:

- **Risk stratification:** low risk (female, 8 year duration, mild disease activity previously)
- **Technique:** High definition

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Ongoing Questions About Screening/Surveillance

- **Why do we do it?**
- **What technique should we use?**
  - What is the optimal method of detecting dysplasia?
  - Random or targeted biopsies?
  - When should chromoendoscopy be performed?
- **When is active surveillance appropriate instead of surgery?**
Most Dysplasia is Visible with White Light

Retrospective assessment of colonoscopies and dysplasia\textsuperscript{1,2}:
- Per lesion sensitivity: 61.6\%-77.3\%
- Per patient sensitivity: 78.3\%-89.3\%


Random Biopsies are of Lower Yield for Dysplasia than Targeted Biopsies

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Proportion surveyed & All patients with BD & No. of studies (no. of patients) & High definition\textsuperscript{a,b} & Chromendoscopy \textsuperscript{a,b} & Standard definition \\
\hline
\hline
No. of studies (no. of patients) & 4 (362) & 7 (1,288) & 11 (1,750) & 11 (1,750) \\
\hline
Identified on targeted biopsies & 15.4\% (93\%-24.5\%) & 11.6\% (8.3\%-18.3\%) & 11.8\% (8.6\%-16.7\%) & 11.8\% (8.6\%-16.7\%) \\
\hline
Identified on random biopsies only & 1.6\% (0.7\%-3.6\%) & 1.2\% (0.8\%-2.0\%) & 2.0\% (1.1\%-6.0\%) & 2.0\% (1.1\%-6.0\%) \\
\hline
\hline
No. of patients with dysplasia identified by each modality & 4 (39) & 7 (158) & 12 (220) & 12 (220) \\
\hline
Identified on targeted biopsies & 90.6\% (90.1\%-95.0\%) & 90.2\% (88.5\%-94.0\%) & 80.4\% (80.0\%-94.0\%) & 80.4\% (80.0\%-94.0\%) \\
\hline
Identified on random biopsies only & 9.4\% (4.1\%-15.9\%) & 9.8\% (6.9\%-15.0\%) & 19.6\% (11.3\%-31.2\%) & 19.6\% (11.3\%-31.2\%) \\
\hline
Proportion of all random biopsy specimens positive for dysplasia & 5 (8730) & 11 (46,522) & 11 (25,238) \\
\hline
Proportion positive for dysplasia & 0.2\% (0.0\%-1.2\%) & 0.1\% (0.0\%-0.3\%) & 0.7\% (0.1\%-0.3\%) & 0.7\% (0.1\%-0.3\%) \\
\hline
\end{tabular}
\caption{Pooled analysis of detection of dysplasia with targeted biopsies and with random biopsies alone in studies of high-definition white-light colonoscopy, chromendoscopy, and standard-definition white-light colonoscopy.}
\end{table}

Case 2:

• A 50 year old male with UC since age 28.
• Maintained on infliximab and azathioprine.
• 3-4 stools per day. Occasional blood and urgency.
• Last colonoscopy 2 years ago
  – Diffuse mild inflammation throughout the colon and rectum
  – Random biopsies performed: No dysplasia

Case 2:

• **Risk stratification:**
  moderate risk (male, 22 year duration, moderate disease activity previously)
• **Technique:** High definition ± chromo
Ongoing Questions About Screening/Surveillance

• Why do we do it?
• What technique should we use?
  – What is the optimal method of detecting dysplasia?
  – Random or targeted biopsies?
  – When should chromoendoscopy be performed?
• When is active surveillance appropriate instead of surgery?

SCENIC meta analysis of 8 trials
- Greater proportion of patients with dysplasia when chromoendoscopy is performed vs standard white light.
  RR=1.8 [1.2-2.6], AR increase=6% [3-9%]

What about High Definition Scopes?

Does dye-spray chromoendoscopy add anything?

Statement 3: When performing surveillance with high-definition colonoscopy, chromoendoscopy is suggested rather than white-light colonoscopy.
(84% agreement; conditional recommendation; low-quality evidence)

No Difference Between High Def Endoscopy, Dye-spraying Chromoendoscopy, and Virtual Chromoendoscopy for Detection of Dysplasia in UC

Detection of Colonic Dysplastic Lesions During IBD Surveillance Colonoscopy

- HDE (n=54)
- DSC (n=49)
- VCE (n=52)

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>HDE</th>
<th>DSC</th>
<th>VCE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with dysplasia</td>
<td>3.6</td>
<td>2.9</td>
<td>5.3</td>
<td>0.53</td>
</tr>
<tr>
<td>Sessile serrated adenoma</td>
<td>19.6</td>
<td>5.9</td>
<td>26.3</td>
<td>0.07</td>
</tr>
<tr>
<td>Tubular adenoma</td>
<td>37.5</td>
<td>20.6</td>
<td>15.8</td>
<td>0.04</td>
</tr>
</tbody>
</table>

- Patients: 2 n=2, 1 n=1

Iacucci M et al. Presented at DDW; May 17, 2015. Abstract 327

University of Chicago Approach to Chromoendoscopy

- Selected patients (not all)
- Clean prep
- Minimal to no inflammation
- Methylene blue preferred
  - 2 10mg/ml vials
  - 250 cc irrigation fluid
- Power wash device
Examples of Chromoscopy in Action

Still images, videos
Examples of pit patterns and histopathology

Identifying a lesion with Methylene Blue
Pseudopolyposis. What is the role of chromoscopy in this situation?

47 yo F Crohn’s colitis in remission. Grandfather with CRC.
38 yo M Crohn’s ileo- pancolitis. This lesion is seen in the sigmoid colon. (white light)

Polyp removed by snare cautery: LGD. Ongoing follow-up with surveillance at 6 months (with chromoscopy), and then annually.

71 yo M indeterminate extensive colitis for 10 years. In remission. This lesion is seen in the sigmoid colon. (narrow band imaging)

Unresectable lesion with HGD: surgery.

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**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&lt;sup&gt;a&lt;/sup&gt; (73%)</td>
<td>7/11&lt;sup&gt;b&lt;/sup&gt; (64%)</td>
</tr>
<tr>
<td>Van den Broek et al. (2011)</td>
<td>Tandem</td>
<td>48</td>
<td>8/11&lt;sup&gt;a&lt;/sup&gt; (73%)</td>
<td>9/11&lt;sup&gt;a&lt;/sup&gt; (82%)</td>
</tr>
<tr>
<td>Ignjatovic et al. (2012)</td>
<td>Parallel group</td>
<td>112</td>
<td>5/56&lt;sup&gt;a&lt;/sup&gt; (9%)</td>
<td>5/56&lt;sup&gt;b&lt;/sup&gt; (9%)</td>
</tr>
</tbody>
</table>

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

<sup>a</sup>Proportion of total dysplastic lesions detected overall; <sup>b</sup>Proportion of patients with at least one dysplastic lesion.

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39 yo with left-sided UC actively inflamed and polyp in right colon: LGD, biopsy around lesion no colitis in region.
FH: father with CRC

Colitis treated aggressively. Follow-up colonoscopy at 6 months with chromoendoscopy, no additional dysplasia. Subsequent annual follow-up.

Endoscopic Mucosal Resection of a Visible LGD Lesion
62 yo M UC >20 years, focal polypoid lesion in sigmoid colon. UC in remission for 10 years.

Endoscopically unresectable despite three separate exams. Surgery performed.

36 yo F with extensive UC for 15 years in remission on 5-ASA.

This lesion is seen in the rectum.
35 yo with long standing colitis presents with this lesion in the distal rectum.

Pathology: polypoid LGD and HGD; no flat dysplasia

Follow-up three months later. Scar tissue without dysplasia. SEPARATE AREA of LGD on random biopsy in rectum.

Surgery. Proctocolectomy reveals no dysplasia. IS THIS SUCCESSFUL PREVENTION?
A 58-year-old female with a personal history of colonic polyps and ulcerative pancolitis, undergoing high risk colon cancer surveillance of colonoscopy.
Sessile polyp in the ascending colon.

Sessile polyp in the ascending colon.
A 52-year-old female with Crohn's disease and previously identified unifocal low-grade dysplasia in the rectum on 2 sequential exams.
A 52-year-old female with Crohn's disease and previously identified unifocal low-grade dysplasia in the rectum on 2 sequential exams

Extensive flat low-grade dysplasia arising in a background of mildly active inflammatory bowel disease

A 74-year-old female with Crohn's disease and recent colonoscopy with polypoid and possibly flat mucosal dysplasia in the hepatic flexure and ascending colon, undergoing colonoscopy.
Focal serrated change in a background of mildly active and quiescent inflammatory bowel disease.
The patient is a 50-year-old female with ulcerative pancolitis for 30 years who was referred after surveillance colonoscopy revealed active inflammation and, by outside interpretation, high-grade dysplasia.
Cecum, adherent mucous: Sessile serrated lesion
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


CASE 2 Follow-up: Endoscopic Mucosal Resection of a Visible LGD Lesion
### Ongoing Questions About Screening/Surveillance

- Why do we do it?
- What technique should we use?
  - What is the optimal method of detecting dysplasia?
  - Random or targeted biopsies?
  - When should chromoendoscopy be performed?
- When is active surveillance appropriate instead of surgery?

### What is the Risk Of Cancer in a Patient with LGD?

- **Synchronous**
  - “Historical”¹: synchronous cancer when LGD found: 19%
  - Chicago, 2015²: synchronous cancer when LGD found: 0%
- **Metachronous**
  - NYC, 2003³: *High* rate of progression to advanced lesions
  - UK, 2006⁴: *Lower* rate of progression to advanced lesions
  - Chicago, 2010⁵: *Lower* rate of progression, especially when polypoid

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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)

Statement 9: 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.
(100% agreement; conditional recommendation; very low-quality evidence)
Active Surveillance Algorithm

Dysplasia

Endoscopic appearance

Flat

Visible by WLE/raised

Grade?

High

Low

Complete endoscopic resection

Multifocal?

Yes

No

Colectomy

Colectomy vs. active surveill follow-up

Colonoscopy ≤6 months and active surveill

Random biopsy or only visible by chromoendoscopy

Summary: An Updated Approach to Surveillance

- The risk of cancer in IBD is now lower than previously described.
- Evolving optical technology has made identification of dysplasia easier.
- Random biopsies for surveillance are of limited utility.
- Not all dysplasia requires immediate colectomy.
- We recommend:
  - Stratify your patients by individual risk factors.
  - Consider chromoendoscopy:
    • if you use SD scopes
    • in higher risk patients
    • previous confirmed dysplasia (flat or raised)
    • lesions found and require clarification
  - Get a second opinion (from IBD endoscopist or surgeon).
Thank You!