Dysplasia in IBD
What You See Is What You Get

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Disclosures

Consulting/Advisory Board/Research Work and Support

Janssen

Genentech
**SPORADIC COLON CANCER**

- Aneuploidy
  - APC
- MSI
  - *k-ras*

- Normal mucosa
- Early adenoma
- Intermediate adenoma
- Late adenoma
- Carcinoma

**COLITIS-ASSOCIATED COLON CANCER**

- Aneuploidy
  - MSI
- p53
- *k-ras*
- APC

- Negative dysplasia
- Indefinite dysplasia
- Low-grade dysplasia
- High-grade dysplasia
- Carcinoma
Dysplasia-Carcinoma Sequence

Normal → Adenoma → Cancer

Colitis → Dysplasia → Cancer
Cumulative Risk of CRC in UC

0.5-1.0% per year after 10 years of disease

Risk of CRC in Crohn’s

Canavan, APT, 2006
Risk of CRC in IBD: Factors that Increase Risk

- Duration >8-10 years
- Extent of colitis:
  - Extensive disease
  - Backwash ileitis
- Family history of colon cancer
- Primary sclerosing cholangitis
- Early age at onset of colitis
- Histologic activity
- Pseudopolyps
- Dysplasia at surveillance
Risk of CRC in IBD: Factors that Decrease Risk

• Prophylactic Colectomy
• Regular doctor visits (and the unknown)
• Surveillance colonoscopy
  • Timely surgery/lesion removal
  • Adjunctive colonoscopic techniques
• Chemoprevention?
  • 5-ASA  
  • UDCA  
  • Folate  
  • Thiopurines  
Cancer Surveillance in Colitis

- Inflammation
  - Initiate screening and surveillance; minimize inflammation

- Dysplasia
- Cancer
  - Intervene to prevent further progression: *polypectomy* or surgery

- Death
Issue 1

• Can we prevent colorectal neoplasia by administering anti-inflammatory medications?
Increased Inflammation Is Associated with Neoplastic Progression

<table>
<thead>
<tr>
<th></th>
<th>Inflammatory Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>2.4</td>
</tr>
<tr>
<td>Controls</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Odds Ratio: 4.7 (1.1-8.5)

Limits: Case-Control Methodology
- No adjustment for changes over time
- Scoring system never previously used

Effect of Histologic Inflammation on Progression to HGD or CRC in Mount Sinai UC Surveillance Cohort

Table 5. Association Between Mean Inflammation Score and End Point After Adjusting for Frequency of Scopes per Year ≥1

<table>
<thead>
<tr>
<th>End point, HR (95% CI)</th>
<th>Any neoplasia (n = 65)</th>
<th>Advanced neoplasia (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IS-mean</td>
<td>1.4 (0.9–2.3)</td>
<td>3.8 (1.7–8.6)</td>
</tr>
<tr>
<td>One or more colonoscopies per year</td>
<td>1.7 (0.9–3.1)</td>
<td>5.4 (1.7–17.0)</td>
</tr>
</tbody>
</table>

NOTE. IS-mean and frequency of colonoscopy were both modeled as time-changing covariates.

Gupta, Gastro 2007
Mesalamine Chemoprevention: Summary of Cancer Studies

### A. Cancer*

<table>
<thead>
<tr>
<th>Study type</th>
<th>Author (Year)</th>
<th>Number</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort</strong></td>
<td>Moody (1996)†</td>
<td>10</td>
<td>0.08 (0.02-0.29)</td>
</tr>
<tr>
<td></td>
<td>Lindberg (2001)†</td>
<td>7</td>
<td>0.28 (0.06-1.42)</td>
</tr>
<tr>
<td><strong>Case-Control</strong></td>
<td>Pinczowski (1994)</td>
<td>102</td>
<td>0.38 (0.20-0.69)</td>
</tr>
<tr>
<td></td>
<td>Eaden (2001)</td>
<td>102</td>
<td>0.47 (0.22-1.00)</td>
</tr>
<tr>
<td></td>
<td>Van Staa (2003)</td>
<td>76</td>
<td>0.54 (0.35-0.86)</td>
</tr>
<tr>
<td></td>
<td>Bernstein (2003)</td>
<td>11</td>
<td>1.22 (0.32-4.62)</td>
</tr>
</tbody>
</table>

*Adjusted summary odds ratio*  
*P value for homogeneity*  

0.51 (0.37-0.69);  
*P*=0.46

Velayos et al. *Am J Gastro* 100:1345, 2005
Chemopreventive Effect of Mesalamines: Small if at All

<table>
<thead>
<tr>
<th></th>
<th>5ASA Exposure</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Use</td>
<td>&gt;2 g/day</td>
<td>Avg Dose</td>
<td></td>
</tr>
<tr>
<td>Any Neoplasia HR (95% CI)</td>
<td>0.86 (0.40-1.82)</td>
<td>0.91 (0.47-1.77)</td>
<td>1.01 (0.80-1.28)</td>
<td></td>
</tr>
<tr>
<td>Advanced Neoplasia HR (95% CI)</td>
<td>0.70 (0.20-2.44)</td>
<td>0.77 (0.22-2.67)</td>
<td>0.92 (0.58-1.47)</td>
<td></td>
</tr>
</tbody>
</table>

*Ullman, CGH 6:1225-30, 2008*
## Thiopurine Chemopreventions: Mount Sinai Experience (n=315)

<table>
<thead>
<tr>
<th></th>
<th>6MP/AZA Exposure</th>
<th>Any Exposure</th>
<th>&gt;25mg/d</th>
<th>Avg Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any Neoplasia HR (CI)</strong></td>
<td></td>
<td>1.30 (0.45-3.75)</td>
<td>0.88 (0.47-1.65)</td>
<td>1.21 (0.70-1.02)</td>
</tr>
<tr>
<td><strong>Advanced Neoplasia HR (CI)</strong></td>
<td></td>
<td>0.88 (0.48-1.59)</td>
<td>1.46 (0.51-4.21)</td>
<td>1.95 (0.82-4.60)</td>
</tr>
</tbody>
</table>

*Matula, CGH 2005*
### Thiopurines Prevent Advanced Colorectal Neoplasia in Patients with IBD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted HR</th>
<th>Adjusted HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopurines</td>
<td>0.25 (0.08-0.84)</td>
<td>0.10 (0.01-0.75)</td>
</tr>
<tr>
<td>5ASA</td>
<td>0.52 (0.25-1.09)</td>
<td>0.56 (0.22-1.40)</td>
</tr>
<tr>
<td>Age</td>
<td>1.05 (1.03-1.08)</td>
<td>1.07 (1.03-1.10)</td>
</tr>
<tr>
<td>Extent &gt; 50%</td>
<td>5.5 (2.05-14.7)</td>
<td>5.3 (1.79-15.8)</td>
</tr>
<tr>
<td>Prior dysplasia</td>
<td>1.07 (0.15-7.88)</td>
<td>0.48 (0.06-3.83)</td>
</tr>
</tbody>
</table>

**Key limitations:**
- Not adjusted for scope exposure
- Disease duration, activity, medications prior to 2001 unknown due to nature of data set
- Timing of TP exposure relative to advanced neoplasia unknown

van Schaik et al. Gut 2011
UDCA Protects Against Neoplasia in PSC Patients

High Dose UDCA (28-30 mg/kg) Associated with Increase Risk of Dysplasia and CRC

Other tidbits:
5ASA HR=1.2 (0.2-23.2)
Duration, extent not sig

Issue 2

- So if I can’t prevent neoplasia, should I just take loads of biopsies at surveillance?
The Limitations of Random Biopsies

- Surface area of colorectum: 1578.1 ± 301.0 cm²
- Surface area of biopsy forceps: 2.2-5 mm²
- Recommended “at least 33 biopsies”
- Percent surface area with this approach: 0.05%-0.1%

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

Dysplasia in UC is Usually Visible with White Light

- “Visible”
  - Polypoid “adenoma-like” lesion
  - Irregular borders “spreading” lesion, not endoscopically resectable (DALM)
  - Mass
  - Stricture

- Optical colonoscopy sensitivity (retrospective studies):
  - Per lesion sensitivity: 61.6%-77.3%
  - Per patient sensitivity: 78.3%-89.3%

Issue 3

• So what if I find dysplasia?
Probability of Finding Cancer

If colectomy done:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Immediately</th>
<th>After some F/U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade 1</td>
<td>3/16 (19%)</td>
<td>17/204 (8%)</td>
</tr>
<tr>
<td>Low-grade 2</td>
<td>2/11 (19%)</td>
<td></td>
</tr>
<tr>
<td>Low-grade 3</td>
<td>2/10 (20%)</td>
<td></td>
</tr>
</tbody>
</table>

1 Bernstein et al. Lancet, 1994
2 Ullman et al. Gastro, 2003
3 Rutter et al, Gastro, 2006
### Progression of LGD to HGD or Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Hospital</th>
<th>LGD (n)</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connell ('94)</td>
<td>St. Mark’s</td>
<td>9</td>
<td>54% @ 5 yrs</td>
</tr>
<tr>
<td>Ullman ('03)</td>
<td>Mount Sinai</td>
<td>46</td>
<td>53% @ 5 yrs</td>
</tr>
<tr>
<td>Ullman ('02)</td>
<td>Mayo Clinic</td>
<td>18</td>
<td>33% @ 5 yrs</td>
</tr>
<tr>
<td>Rutter ('06)</td>
<td>St. Mark’s</td>
<td>36</td>
<td>25% @ 5 yrs</td>
</tr>
<tr>
<td>Lindberg ('96)</td>
<td>Huddinge</td>
<td>37</td>
<td>35% @ 20 yrs</td>
</tr>
<tr>
<td>Lim ('03)</td>
<td>Leeds, UK</td>
<td>29</td>
<td>10% @ 10 yrs</td>
</tr>
<tr>
<td>Befrits ('02)</td>
<td>Karolinska</td>
<td>60</td>
<td>2% @ ~10 yrs</td>
</tr>
</tbody>
</table>
• 46 patients with flat LGD at index from 1994-2000; non-protocol-based surveillance
• F/U of all surveillance examinations
• Progression defined as HGD or CRC
• Is unifocal LGD a less dangerous subset?

Ullman, Gastro, 2003
Timelines: fLGD $\rightarrow$ CRC (N=7)

C  CRC
H  HGD
L  LGD
I  IND
-  No Dys

Initial fLGD

Ullman et al. Gastro, 2003
Low-Grade Tubulo-Glandular Adenocarcinoma (LGTGA)

- Well-differentiated adenocarcinoma with distinct histological features:
  - rounded, oval or tubular glands
  - minimal desmoplastic reaction
  - minimal intraluminal necrosis
  - low-grade nuclear cytology

Low-Grade Tubulo-Glandular Adenocarcinoma (LGTGA)

- Frequent association with IBD
- Accounts for 11% of IBD-associated CRC
- Some patients have multiple LGTGA
- Occurs in setting of UC or Crohn’s colitis
- Infrequent pre-operative diagnosis
- Direct derivation from LGD

What about Polypoid LGD?
Proposed Classification for IBD-Related Colorectal Neoplasms

• Polypoid Neoplasms
  – Sessile
  – Pedunculated

• Non-polypoid neoplasms
  – Slightly elevated, table top flat (Paris IIa)
  – Depressed (Paris IIc)
  – Flat, completely flat (Paris Iib)
  – Unrecognized/occult

• Endoscopically resectable or unresectable
DALM vs. Adenoma

• No clear-cut distinction

• Akin to Justice Stewart’s definition of pornography?
OK for Polypectomy

Rubin, Engelsgjerd, Gastro 1999; Odze 2004
# Colectomy vs. Polypectomy and continued surveillance

<table>
<thead>
<tr>
<th>Flat dysplasia or adenocarcinoma present</th>
<th>Colectomy</th>
<th>Polypectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Endoscopic Appearance</th>
<th>Broad-based/mass Irregular Ulcerated Plaque-like Constricting</th>
<th>Small Discrete</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amenable to polypectomy</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
# Probability of Finding Cancer

**Immediate Colectomy** | **After some F/U**
--- | ---
Bernstein, 1994, DALM | 17/40 (43%) | 1/24 (7.5 yrs)
Odze, 2004, P-DALM | 0/48 | 0/24 (8%)
Rubin, 1999, D-polyps | 0/48 | 0/24 (8%)
Engelsgjerd, 1999, P-DALM | 2/52 (4%)/5 yrs | 2/52 (4%)/5 yrs
Rutter, 2006, adenoma | 30% | 30%
Rutter, 2006, DALM-L | 30% | 30%
Rutter, 2006, DALM-H | 33% | 33%
Flat “worse” than raised LGD

Goldstone, GIE 2012
Issue 4

• Do adjunctive endoscopic techniques reduce the risk of colorectal cancer morbidity and mortality in IBD?
• Is the old way of performing surveillance alive or dead?
Prospective Studies Comparing Chromoendoscopy to SD White Light

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Method</th>
<th>Increased Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiesslich et al (2003)</td>
<td>165</td>
<td>MB</td>
<td>3-fold (lesions)</td>
</tr>
<tr>
<td>Rutter et al (2004)</td>
<td>100</td>
<td>IC</td>
<td>4.5-fold (lesions)</td>
</tr>
<tr>
<td>Kiesslich et al (2007)</td>
<td>161</td>
<td>MB and EM</td>
<td>4.75-fold (lesions)</td>
</tr>
<tr>
<td>Marion et al (2008)</td>
<td>102</td>
<td>MB</td>
<td>1.5 fold (patients)</td>
</tr>
</tbody>
</table>
10 mL of Methylene Blue x 2
Mix in 200 mL water
Figure 3. (A) Within previously unremarkable colonic mucosa, a discretely elevated lesion is visible after staining (arrows). (B) On closer inspection, an irregular surface structure is visible. On histologic analysis, this lesion was identified as low-grade intraepithelial neoplasia.

Figure 4. (A) The native colonic mucosa shows areas of focal erythema. (B) After CE, a flat lesion is seen that correlates with high-grade intraepithelial neoplasia on histology.
Small lesions: lift and cut (apologies to Trac II)
HD Chromo vs HD White Light:

- One prospective study: Tandem surveillance in 75 patients using indigo carmine, 2009-2013

<table>
<thead>
<tr>
<th></th>
<th>Patients with Dysplasia</th>
<th>Dysplastic Lesions</th>
<th>Non-polypoid Dysplastic Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD Chromo</td>
<td>21.3% (16/75)</td>
<td>100% (22/22)</td>
<td>9.3% (7/75)</td>
</tr>
<tr>
<td>HD WL</td>
<td>9.3% (7/75)</td>
<td>45.4% (10/22)</td>
<td>1.3% (1/75)</td>
</tr>
</tbody>
</table>

p<0.02 for all comparisons

Picco, IBD 2013
But Does Detecting “More Dysplasia” Matter? (How Much Are We Missing?)

- Mount Sinai Surveillance Database
- 1183 dysplasia surveillance examinations of patients with extensive UC
- # of cases with CRC without prior dysplasia?
- 1 (0.085%)
- The old system wasn’t all that bad

Ullman, ACG 2007
On the other hand . . .
Missed lesions more common in IBD than in general populations

• SEER database reviewed 1998-2005
  – 55,008 CRC patients
    ○ 304 Crohn’s, 544 UC

<table>
<thead>
<tr>
<th></th>
<th>Miss Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-IBD</td>
<td>5.8%</td>
</tr>
<tr>
<td>Crohn’s</td>
<td>15.1%</td>
</tr>
<tr>
<td>UC</td>
<td>15.8%</td>
</tr>
</tbody>
</table>

Wang Am J Gastro 2013
Beware the “Will Rogers Phenomenon”: Stage Migration

• “When all the Okies left Oklahoma and moved to California, they raised the average *intelligence* level of both states.”

• Stage Migration in Lung Cancer with CT: improved survival at every stage without changing overall survival (*Feinstein, NEJM, 1985*)

• Prognosis at every level in colitis-dysplasia-carcinoma sequence will change with chromo or any other good adjunct
Needed with Advanced Endoscopic Techniques

• Longitudinal studies
• Agreement of end-points worth achieving
  – Dysplasia Yield?
  – Cancers?
  – Cancer mortality/morbidity?
  – Cost?
  – Intervals between colonoscopies?
Challenges to Chromoendoscopy

• 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
Consider Chromoendoscopy for:

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

<table>
<thead>
<tr>
<th>Organization</th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGA</td>
<td>“..chromoendoscopy with targeted biopsies is recommended as an alternative to random biopsies for endoscopists who have expertise with this technique”</td>
</tr>
<tr>
<td>ACG</td>
<td>“Given the increased yield of chromoendoscopy, it may be of value in follow-up of the ‘higher-risk’ patient (i.e. patients with indefinite or known dysplasia not proceeding to colectomy…”</td>
</tr>
<tr>
<td>ASGE</td>
<td>“While promising, chromoendoscopy has not yet been adopted in routine practice.”</td>
</tr>
<tr>
<td>BSG</td>
<td>“Pancolonic dye spraying with targeted biopsy of abnormal areas is recommended.”</td>
</tr>
</tbody>
</table>
SCENIC Recommendations

- Chromo is preferable to WL
- HD is preferable to SD
- Chromo-HD preferable to Chromo SD
- No role for other methodologies
- All dysplasia should be removed
SCENIC Limitations

- No longitudinal chromo, HD, or chromo-HD studies \(\rightarrow\) No known benefits

- Huge cost
  - Training
  - Equipment
Is the Curve Changing with Surveillance?

Clear the Colon

- The purpose of a surveillance examination is to identify neoplastic polyps
- Remove all neoplasia
- If unable, refer for colectomy
- Non-targeted biopsies optional?
Acknowledgements

- Steve Itzkowitz
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- Robert Goldstone
- Noam Harpaz

- NIH
- CCFA
- ACG
Thank You!