Managing Colorectal Dysplasia and Cancer in Inflammatory Bowel Disease

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Overview

• Pathogenesis/molecular markers
• Risk factors, ‘classic’ and ‘new’
• Protective factors
  – Chemoprevention: is it real?
  – Surveillance
• Standard surveillance colonoscopy
• New techniques
  – Chromoendoscopy
  – Narrow band imaging
  – Confocal endomicroscopy
Mutation Markers in Sporadic vs IBD-Related CRC

Sporadic Colon Cancer

- Normal Mucosa
- Early Adenoma
- Intermediate Adenoma
- Late Adenoma
- Carcinoma

- APC
- Aneuploidy
- Methylation
- Sialyl-Tn
- MSI
- k-ras
- COX-2
- c-src
- DCC/DPC4
- p53
- LOH

Colitis-Associated Colon Cancer

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

- APC
- P53 LOH
- DCC
- c-src
- k-ras

Itzkowitz S. Gastroenterol Clin N Am 2006; 35:553
# Methylation Markers: EYA4 Methylation in UC-Dysplasia/CRC

<table>
<thead>
<tr>
<th>Group</th>
<th>EYA4</th>
<th>95% CI</th>
<th>hMLH1</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflamed</td>
<td>0/14 (0%)</td>
<td>0-22</td>
<td>0/9</td>
<td>0-30</td>
</tr>
<tr>
<td>Surveillance neg</td>
<td>0/22 (0%)</td>
<td>0-14</td>
<td>0/6</td>
<td>0-30</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>6/9 (67%)</td>
<td>35-87</td>
<td>0/9</td>
<td>0-40</td>
</tr>
<tr>
<td>CRC</td>
<td>19/22 (87%)</td>
<td>67-96</td>
<td>0/9</td>
<td>0-30</td>
</tr>
</tbody>
</table>

TNF Polymorphisms in UC-CRC

• DNA extracted from paraffin-embedded tissue of 114 UC-CRC and 114 sporadic CRC (matched on age, gender, duration, extent)
  • 5 TNF-α polymorphisms studied
  • -308 (G→A) SNP more common in UC-CRC (43% vs 17%, p<0.0001)
  • Perhaps alterations in genes that modulate inflammation also affect CRC risk?

HLA Alleles in UC-CRC

• Same case-control design as before (114 UC-CRC, 114 UC controls)
• DR1, DR7, DQ5 protective
• DR13, DR17, DQ2 risk factor
• Higher loss of expression of HLA-DR protein in cases vs controls
• Further evidence that the basal level of gut inflammation, regulated by genetic factors, influences CRC risk?

Risk of Colorectal Cancer in UC Meta-Analysis

Eaden: Gut 2001; 48:526
Cumulative Risk of CRC Among 376 UC Patients From Olmsted County, Minnesota, 1940-2001

Cumulative incidence of colorectal cancer (%)

2 patients diagnosed with IBD-CRC within 30 days of IBD diagnosis excluded

25-year cancer risk: 2.0% (vs. 2.3% expected based on Iowa SEER rates) p = 0.55, log-rank

Cumulative Risk of Colorectal Dysplasia Among 684 IBD Patients From Olmsted County, Minnesota, 1940-2001

Cumulative Risk of Proctocolectomy Among 692 IBD Patients From Olmsted County, Minnesota, 1940-2001

Comprehensive Meta-Analysis of the Risk of CRC in UC and Crohn’s

- 48 studies included in the meta-analysis
- Included both population based and referral centers
- Included 131,743 persons-years of follow up
- Overall cumulative risk at 10, 20 and 20+ years is 1%, 3% and 7%
- Rate higher in referral centers and those with extensive disease

Lutgens MW, et al. DDW 2008: #194
Risk Factors for IBD-Related Colorectal Cancer

• ‘Classic’ risk factors
  – Increased extent (i.e., pancolitis vs. proctitis)
  – Increased duration

• ‘Newer’ risk factors
  – Primary sclerosing cholangitis
  – Family history of CRC
  – Backwash ileitis?
  – Severity of inflammation?
Relative Risk of CRC Based on Extent of UC

## Crohn’s Disease
CRC Risk Depends on Colonic Involvement

<table>
<thead>
<tr>
<th>Extent</th>
<th>SIR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileal</td>
<td>1.0 (0.1-3.4)</td>
</tr>
<tr>
<td>Ileocolonic</td>
<td>3.2 (0.7-9.2)</td>
</tr>
<tr>
<td>Colonic</td>
<td>5.6 (2.1-12.2)</td>
</tr>
<tr>
<td>Other</td>
<td>1.2 (0-5.9)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2.5 (1.3-4.3)</strong></td>
</tr>
</tbody>
</table>

* Standardized incidence ratio (relative risk estimate, observed vs expected)

Ekbom et al, Lancet 1990
Is PSC a Risk Factor for Dysplasia and CRC in UC?

- Most but not all studies (case-control, cohort) suggest that PSC is a risk factor for dysplasia and cancer
- Difficult studies to perform
- Mechanism of action unclear
  - May be a marker for quiescent but longstanding pancolitis
  - Role of fecal bile acids?
Overall Probability of Colorectal Cancer or Dysplasia from Observational Start Date in PSC-IBD Cases vs CUC Controls

Years from index date

Cases

Controls

%

0 1 2 3 4 5 6 7 8 9 10

P=0.0571

Loftus EV et al, Gut 2005
Is Family History of CRC a Risk Factor?

- IBD patients from Stockholm, Uppsala, Swedish inpatient register, 1955-95 (n = 19,876)
  - 561 had family hx (1st degree) of CRC (3%)
  - 143 cases of CRC during 169,000 person-years follow-up
  - 13 had family hx of CRC (9%)
  - RR of CRC in those with fam hx was 2.0 in UC, 3.7 in Crohn’s

Askling et al, Gastroenterology 2001
Is Family History of CRC a Risk Factor?

- 2 referral center-based studies also suggest that family history is a risk factor
  - Mayo study: RR 2.3 for first-degree
  - U.K. study: RR 5.0 for any, 3.5 for first-degree

Inflammation May Be a Risk Factor For Colorectal Neoplasia

• Case-control study from St Mark’s
  — 68 CUC with dysplasia/CA
  — 136 CUC without
• Endoscopic and histologic inflammation score was a risk factor
• Multivariate analysis: histologic score was a risk factor (OR, 4.7; 95% CI, 2.1 – 10.5)

Increased Inflammatory Activity: Independent Risk Factor for Dysplasia/CRC in UC

<table>
<thead>
<tr>
<th>Multivariate Analysis</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Categorical model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 vs 0–1</td>
<td>4.9</td>
<td>1.7–14.3</td>
<td>0.004</td>
</tr>
<tr>
<td>3–5 vs 0–1</td>
<td>7.1</td>
<td>1.7–29.8</td>
<td>0.007</td>
</tr>
<tr>
<td>Male gender</td>
<td>5.7</td>
<td>1.9–17.1</td>
<td>0.002</td>
</tr>
</tbody>
</table>

- A greater degree of histologic inflammation was associated with greater odds for CRC/dysplasia in UC
- AZA/6-MP and mesalamine therapies were protective against neoplasia development

Protective Factors for Colorectal Cancer in IBD

- Chemoprevention
  - 5-ASA
  - Ursodeoxycholic acid (in PSC-IBD)
  - Folate?
  - ASA/NSAIDs?
- Colonoscopy
5-ASA Chemoprevention: Proposed Mechanisms

- Decrease pro-inflammatory cytokines
- COX inhibition
- NOS inhibition
- NFκβ inhibition
- PPAR-γ activation
- Oxygen free radical scavenger
- Reduce activity of Wnt/β-catenin pathway
**Meta-Analysis:** Any 5-ASA Use and CRC

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moody (1996)</td>
<td>10</td>
</tr>
<tr>
<td>Lindberg (2001)</td>
<td>7</td>
</tr>
</tbody>
</table>

**Case-Control**

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pinczowski (1994)</td>
<td>102</td>
</tr>
<tr>
<td>Eaden (2001)</td>
<td>102</td>
</tr>
<tr>
<td>Van Staa (2003)</td>
<td>76</td>
</tr>
<tr>
<td>Bernstein (2003)</td>
<td>11</td>
</tr>
</tbody>
</table>

**Pooled odds ratios**

OR: 0.40 (0.20-0.83)

![Graph showing odds ratios for lower and higher risk cancers across different studies.]

Velayos FS et al, Am J Gastroenterol 2005;100:1345
# Meta-Analysis: Definition Of 5-ASA Use And Colorectal Cancer / Dysplasia

## Duration of Use

<table>
<thead>
<tr>
<th>Cases</th>
<th>Definition</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>&gt; 6 mo</td>
<td>Lashner (1997)</td>
</tr>
<tr>
<td>50</td>
<td>&gt; 6 mo</td>
<td>Lindberg (2001)</td>
</tr>
<tr>
<td>102</td>
<td>&gt; 3 mo</td>
<td>Pinczowski (1994)</td>
</tr>
<tr>
<td>11</td>
<td>&gt; 2 mo</td>
<td>Bernstein (2003)</td>
</tr>
<tr>
<td>68</td>
<td>&gt; 3 mo</td>
<td>Rutter (2004)</td>
</tr>
</tbody>
</table>

### Pooled Odds Ratios

**OR: 0.91 (0.37-2.26)**

## Regular Use

<table>
<thead>
<tr>
<th>Cases</th>
<th>Definition</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Compliant</td>
<td>Moody (1996)</td>
</tr>
<tr>
<td>102</td>
<td>Compliant</td>
<td>Eaden (2001)</td>
</tr>
<tr>
<td>76</td>
<td>50% Rx filled</td>
<td>Van Staa (2003)</td>
</tr>
</tbody>
</table>

### Pooled Odds Ratios

**OR: 0.28 (0.10-0.81)**

## Average Dose

<table>
<thead>
<tr>
<th>Cases</th>
<th>Definition</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>M ≥ 1.2 gm</td>
<td>Eaden (2001)</td>
</tr>
<tr>
<td>31</td>
<td>S ≥ 2 gm</td>
<td>Eaden (2001)</td>
</tr>
<tr>
<td>26</td>
<td>M ≥ 1.2 gm</td>
<td>Rubin (2003)</td>
</tr>
</tbody>
</table>

### Pooled Odds Ratios

**OR: 0.37 (0.14-0.97)**

---

## UC-CRC: Effect of IBD Medications
### Mayo Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 188)</th>
<th>Controls (n = 188)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of 5-ASA therapy, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>83 (44)</td>
<td>60 (32)</td>
<td>1.0</td>
<td>ref</td>
</tr>
<tr>
<td>1 - 5 years</td>
<td>38 (20)</td>
<td>47 (25)</td>
<td>0.5</td>
<td>0.3 - 0.9</td>
</tr>
<tr>
<td>6 - 10 years</td>
<td>34 (18)</td>
<td>39 (21)</td>
<td>0.6</td>
<td>0.3 - 1.1</td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>33 (18)</td>
<td>42 (22)</td>
<td>0.6</td>
<td>0.3 - 1.0</td>
</tr>
<tr>
<td><strong>Corticosteroid use &gt; 1 year, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>9 (5)</td>
<td>31 (17)</td>
<td>0.2</td>
<td>0.1 – 0.5</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>5 (3)</td>
<td>21 (11)</td>
<td>0.2</td>
<td>0.1 – 0.6</td>
</tr>
<tr>
<td>Immunomodulator therapy, n (%)</td>
<td>7 (4)</td>
<td>4 (2)</td>
<td>2.1</td>
<td>0.7 - 7.2</td>
</tr>
</tbody>
</table>

Velayos FS et al, Gastroenterology 2006; 130:1941-6.
Cancer & Dysplasia Risk Factors

- In a population-based nested case-control study from Olmsted County and Copenhagen County:
  - Risk factors
    - PSC
    - Markers of disease activity
    - Medication use
  - Protective factors
    - None noted

Ursodeoxycholic Acid in PSC-UC: University of Washington

OR for dysplasia, 0.1 (0.03-0.6)

Tung et al, Ann Intern Med 2001;134:89-95
Mayo RCT of UDCA vs Placebo: Survival Free of Dysplasia or Cancer in PSC-UC

- 10-year rate of CA/dysplasia: 10% urso, 35% placebo
- RR of cancer or dysplasia, 0.26 (0.07-0.99)

Pardi DS et al, Gastroenterology 2003; 124: 889
• Case-control study

• 98 patients with UC
  – Disease proximal to splenic flexure

• Duration: ≥8 years

• 40% of patients used folic acid ≥6 months

• Result: Although not statistically significant, folate reduced neoplasia risk in dose-dependent manner

Surveillance Colonoscopy

- Performed in an attempt to detect pre-cancerous lesions, or early cancers, and reduce mortality due to CRC
- Many case series and reports
- But
  - Is there a benefit?
  - Does it prevent cancer?
  - Or cancer-related death?
Surveillance Colonoscopy Reduces CRC Mortality in UC

Nested case-control study
- Cases: 40 patients with UC who died of CRC
- Controls: 102 living, matched patient with UC

Relative cancer risk
- No colonoscopy: 1.0
- 1 colonoscopy: 0.43 (95%, CI 0.05–3.76)
- ≥2 colonoscopies: 0.22 (95%, CI 0.03–1.74)

CRC, colorectal cancer; CI, confidence interval

Surveillance Colonoscopy Associated With Incremental Stepwise Protection Against CRC

Velayos FS et al. Gastroenterology. 2006;130:1941.

OR, odds ratio

<table>
<thead>
<tr>
<th>Number of Surveillance Colonoscopies</th>
<th>Patients (%)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>48</td>
<td>1.0</td>
<td>0.3–0.8</td>
</tr>
<tr>
<td>1–2</td>
<td>32</td>
<td>0.5*</td>
<td>(0.3–0.8)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>21</td>
<td>0.2*</td>
<td>(0.1–0.5)</td>
</tr>
</tbody>
</table>

*P<0.05

OR, odds ratio

Velayos FS et al. Gastroenterology. 2006;130:1941.
Surveillance Vs. Prophylactic Colectomy Vs. Observation: Decision Analysis

- Prophylactic colectomy was best option
- Surveillance every year, colectomy for LGD was 2nd best option
- Costs are high:
  - Every 2 yrs: $159,000 per life-year saved
  - Every 1 yr: $247,000 per life-year saved

Provenzale et al, Am J Gastroenterol 1998;93:872-80
Surveillance Practice Guidelines: Standard of Care

- American College of Gastroenterology
- American Cancer Society
- US Preventive Services Task Force
- Multi-Society Task Force on CRC (AGA, ACG, ASGE)
- American College of Radiology
- Crohn’s and Colitis Foundation

Kornbluth AA & Sachar DB. Am J Gastroenterol 2004;99:1371-85
Winawer SJ et al. Gastroenterology 2003;124:544-60
When to Begin?

• Frequency of surveillance colonoscopy not defined, every 1-2 years suggested

• Ulcerative Colitis
  – Extensive and left-sided disease: 8-10 years after onset
  – Proctitis: not necessary
  – PSC: immediately

• Crohn’s Disease
  – Extensive colonic: 8-10 years after onset
### How Many Biopsies Are Necessary?

<table>
<thead>
<tr>
<th></th>
<th>Dysplasia</th>
<th>Cancer</th>
<th>Dysplasia or Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>90% conf</strong></td>
<td>33</td>
<td>34</td>
<td>11</td>
</tr>
<tr>
<td><strong>95% conf</strong></td>
<td>56</td>
<td>64</td>
<td>18</td>
</tr>
</tbody>
</table>

Rubin et al, Gastroenterology 1992
Mayo Rochester Protocol for Surveillance Biopsies (assumes no polyps)

• Minimum of 32 biopsies total
• 4 bottles, 8 pieces per bottle
  – Cecum/ascending
  – Transverse
  – Descending/proximal sigmoid
  – Rectosigmoid
Take Your Time!
Part 1

- We **strongly** prefer 2 biopsies per pass, not 4
  - Mayo study of biopsy quality by pathologists blinded to 2-bite versus 4-bite
  - Biopsy quality significantly lower with the 4-bite method (only 66% satisfactory versus 89% with 2-bite)
  - Biopsies are more superficial with 4-bite

• Study of 635 Mayo surveillance colonoscopies for IBD over 23-month period (2002-3)
  — 3.8% flat dysplasia
  — 1.9% polypoid dysplasia
  — 4.4% sporadic adenoma

• Among individual endoscopists (n=59), dysplasia detection rate varied from 0% (n=41) to 47%
Take Your Time!
Part 3

• Correlation between endoscopy time and dysplasia detection rate was weak but highly significant
• For every additional minute, dysplasia detection rate increased 3.5%
• No correlation between number of biopsies and dysplasia rate

What to Do With Biopsy Findings?

• Summary of 10 prospective colonoscopic surveillance studies (1225 UC pts)
• Initial surveillance:
  - No dysplasia: 2.4% develop HGD/DALM/CA
  - Indefinite: 18% develop HGD/DALM/CA
  - Low-grade: 29% develop HGD/DALM/CA
  - High-grade: 33% develop CA
  - DALM: 43% have synchronous CA

Bernstein et al, Lancet 1994
### 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. Marks</td>
<td>9</td>
<td>54% @ 5 y</td>
</tr>
<tr>
<td>Ullman (‘03)</td>
<td>Mount Sinai</td>
<td>46</td>
<td>53% @ 5 y</td>
</tr>
<tr>
<td>Ullman (‘02)</td>
<td>Mayo Clinic</td>
<td>18</td>
<td>33% @ 5y</td>
</tr>
<tr>
<td>Lindberg (‘96)</td>
<td>Huddinge</td>
<td>37</td>
<td>35% @ 20 y</td>
</tr>
<tr>
<td>Lim (‘03)</td>
<td>Leeds, UK</td>
<td>29</td>
<td>10% @ 10 y</td>
</tr>
<tr>
<td>Befrits (‘02)</td>
<td>Karolinska</td>
<td>60</td>
<td>2% @ ~10 y</td>
</tr>
</tbody>
</table>
Polypoid Dysplasia

- Dysplasia-Associated Lesion or Mass ("DALM")
  - Formerly an absolute indication for colectomy (high rate of synchronous CRC)
- Several studies suggest that certain polypoid dysplastic lesions can be safely followed:
  - Amenable to endoscopic therapy
  - Surrounding biopsies show no flat dysplasia
Polypectomy for Polypoid Dysplasia

German private practices: 60 had biopsies only, 87 had polypectomy

Survival free of dysplasia

Survival free of cancer

Vieth, M et al. Gut 2006;55:1151-1155
Cumulative Probability of Polypoid Disease in Polypectomy Patients: Mayo Clinic (n = 77)

Kisiel JB, et al. DDW 2007
Cumulative Probability of CRC/HGD/Flat LGD in Polypectomy Patients: Mayo Clinic (n = 77)

Kisiel JB, et al. DDW 2007
Most Dysplasia Is NOT Flat

• St Mark’s study, 1988-2002
• 525 UC patients (2,204 scopes)
• 110 dysplastic lesions in 56 pts
  — 85 (77%) visible at endoscopy
  — 25 (23%) not visible ("flat")
• Endoscopic appearance predicts risk:
  — Pseudopolyps: OR, 2.3 (1.3 – 4.1)
  — Strictures: OR, 4.6 (1.03 – 21)
  — Normal endoscopic: OR, 0.4 (0.2 – 0.7)

Pit Pattern Classification by Kudo et al

A

I
II

Non-neoplastic pattern

IIIs IIIL IV V

Neoplastic pattern

B

Example type I

Example type IV

Kiesslich, R et al. Gut 2004;53:165-167
Chromoendoscopy: The Future?

German RCT: 165 UC randomized to standard surveillance vs chromo

Pseudopolyp, normal pit pattern  Hyperplastic polyp, stellate pattern

Kiesslich et al, Gastroenterology 2003;124:880-8
Methylene Blue Chromoendoscopy

Dysplasia detection rate was triple in the chromo group
44 minutes chromo vs 35 minutes standard surveillance

Low grade dysplasia
irregular pit pattern

Kiesslich et al, Gastroenterology 2003;124:880-8
“Flat” mucosa is no longer flat
High-grade dysplasia
Chromoendoscopy with Methylene Blue

Before

HGD

After

Cancer

Methylene Blue Chromoendoscopy

Regular crypt openings

Pseudopolyp:
overlying mucosa similar to
surrounding mucosa

Kiesslich R et al. Eur J Gastroenterol Hepatol 2005;8:793
Methylene Blue Chromoendoscopy: High-Grade Dysplasia

This flat lesion was invisible to white light

Methylene blue pit pattern IIIS

Kiesslich R et al. Eur J Gastroenterol Hepatol 2005;17:793
Depressed Colon Cancer

Conventional
white light
Flat lesion, central depression

Indigo carmine
pit pattern V

Indigo Carmine Chromoendoscopy

After dye washout

After indigo carmine: type IV

Indigo carmine alone

After crystal violet

Hata, K et al. Gut 2004;53:1722