Colon Cancer in IBD: Detection, Prevention and Management

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Learning Objectives

• Review the relationship between inflammation and colorectal cancer in chronic ulcerative colitis.
• Provide an update of evidence of the risk factors and prevention strategies related to cancer and IBD.
• Provide practical advice for the incorporation of chromendoscopy into surveillance programs.
Progress in IBD-Cancer

THEN

• CRC in UC common
• Dysplasia-cancer relationship identified
• Disease activity is not relevant to risk
• Random biopsies performed
• Any dysplasia → colectomy
**Progress in IBD-Cancer**

**THEN**
- CRC in UC common
- Dysplasia-cancer relationship identified
- Disease activity is not relevant to risk
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**NOW**
- CRC in UC less frequent
- Distinction between flat and raised and polypoid dysplasia
- Inflammation is a major risk factor, other risks identified
- Directed biopsies can be performed
- Some dysplasia can be followed safely

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**The IBD-Cancer Prevention Formula**

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

Accurate Risk Identification:
- Which patients?
- How to quantify risks?

Accurate Detection of Precancer:
- Understanding of predictive value of lesions
- Colonoscopy imaging
- Accurate biopsies
- Reliable pathology

Effective Prevention Strategies:
- Patients and physicians implement strategies
- Colectomy
- Polypectomy
- Chemoprevention

Outcome of interest:
- ↓ CRC
- ↓ Mortality
- ↓ Colectomy
- ↑ Quality of Life
Postulated Causes of CRC in IBD

Oxidative stress

INFLAMMATION

Environmental effects

- Bacterial changes

Genetic alterations


Inflammation Is Associated With Increased Neoplasia Risk in UC

<table>
<thead>
<tr>
<th>Author</th>
<th>Location</th>
<th>Design</th>
<th>Patients</th>
<th>Histologic inflammation</th>
<th>Risk (OR or HR)</th>
<th>p Value</th>
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</thead>
<tbody>
<tr>
<td>Rutter</td>
<td>London</td>
<td>Case-control</td>
<td>68 cases 136 controls</td>
<td>Histologic inflammation (retrospective)</td>
<td>OR 4.69 (2.10-10.48)</td>
<td>&lt;0.001</td>
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<tr>
<td>Gupta</td>
<td>New York</td>
<td>Cohort</td>
<td>418 pts 65 neoplasia 15 advanced neoplasia</td>
<td>Advanced neoplasia</td>
<td>IS-mean HR 3.0 (1.4-6.3)</td>
<td>&lt;0.05</td>
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<tr>
<td></td>
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<td></td>
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<td>IS-binary HR 3.4 (1.1-10.4)</td>
<td>&lt;0.05</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IS-max HR 2.2 (1.2-4.2)</td>
<td>&lt;0.05</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>IS-mean HR 1.4 (0.9-2.3)</td>
<td>NS</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IS-binary HR 1.7 (0.9-3.1)</td>
<td>NS</td>
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<td>IS-max HR 1.0 (0.7-1.5)</td>
<td>NS</td>
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<tr>
<td>Rubin</td>
<td>Chicago</td>
<td>Case-control</td>
<td>59 cases 141 controls</td>
<td>Average histologic inflammation (regraded)</td>
<td>OR 4.9 (1.7-14.8)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.1 (1.7-29.8)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

OR, odds ratio; HR, hazard ratio; NS, not significant

Risks of Dysplasia or CRC in UC

- Longer duration of disease
- Greater extent of disease
- Family history of CRC\(^1,2\)
- Primary sclerosing cholangitis\(^3\)
- Younger age of diagnosis (?)
- Backwash ileitis (?)
- Mass/stricture
- Pseudopolyps
- Increased activity of disease
- Male gender


Should we combine or compound these risks and adjust prevention strategies accordingly?

Cumulative Risk of Developing CRC in IBD
Prior Meta-Analyses

Ulcerative Colitis

Crohn’s Colitis

- Upper CL
- Cumulative risk of CRC
- Lower CL

Cumulative Probability (%)

Time From Diagnosis (y)

Cumulative Probability (%)

Time From Diagnosis (y)

CL=confidence limit.

Incidence and Mortality of CRC in IBD
Kaiser Population

- 5053 CD; 9822 UC patients
- 4,459,950 without IBD
- 14.5 y follow-up
- 1.6-fold higher risk of CRC than non-IBD
- Mortality 2.3x in CD and 2.0x in UC than non-IBD


An Updated Meta-Analysis of the Risk of CRC in IBD

- 48 studies
- Population based and referral centers
- 131,743 persons-years of follow up
- Cumulative risk at 10, 20 and 20+ years is 1%, 3% and 7%
- Rate higher in referral centers and those with extensive disease

Current U.S. Surveillance Guidelines (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

Problems with the Current U.S. Surveillance Guidelines

• No prospective evidence of mortality benefit (or even CRC benefit)

• Difficulties with pathology diagnosis of dysplasia

• Don’t stratify risk based on compounded risk factors (including inflammation)

• Haven’t adjusted for improved technology or understanding of natural history
When should you have a second pathologist review your biopsies?

No dys  IND  LGD  HGD  Cancer

K=0.51  Good
K=0.18  Poor
K=0.36  Fair
K=0.54  Good

Expert review of digitized slides

The Limitations of Random Biopsies
The Limitations of Random Biopsies

- Surface area of colorectum: $1578.1 \pm 301.0 \text{ cm}^2$
- Surface area of biopsy forceps: $2.2 - 5 \text{ mm}^2$
- 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

- "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%

“Progression” of Neoplasia in UC
Some Dysplasia can be Followed

Raised and flat dysplasia in all patients

- Raised dysplasia
- Flat dysplasia

n=41

Chromoendoscopy is Superior to White Light Colonoscopy

<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>
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<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>
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<tr>
<td>Hurlstone (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>
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<tr>
<td>Kiesslich (2007)</td>
<td>University of Mainz, Germany</td>
<td>161</td>
<td>Confocal endomicroscopy</td>
<td>19</td>
<td>4</td>
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<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>
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<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
- Marion¹
  - Follow-up with colectomy specimens
  - 5 of original 102 had colectomy due to unresectable LGD
  - No CRC

Suggested Approach to Chromoendoscopy in 2012

• **WHO:**
  – patients previous confirmed dysplasia (flat or raised) and high risk
  – Lesions found and require clarification
  – Minimal inflammation

• **PREP:** CLEAN

• **TYPE:** Methylene blue diluted

• **HOW:**
  – Raised lesions AND abnormal pit patterns

• **FOLLOW-UP:** Varies…
Gravity

Approach to Polypoid Dysplasia in IBD

Dysplasia in Colitis

Endoscopic appearance
- Flat
- Polyp

Grade?
- High
- Low

Complete endoscopic resection

Multifocal?
- Yes
- No

Colectomy
Colectomy vs. aggressive follow-up
Colonoscopy ≤6 months

Update on Chemoprevention (Primary Prevention)

- 5-ASA: inconsistent results\(^1\)
- Thiopurines: associated with reduced risk\(^2\)
- Anti-TNF: limited evidence so far\(^3\)
- Problems:
  - Inadequate duration of follow-up or limited long-term data on drug use
  - Many studies fail to adjust for confounders
- No agents result in altered surveillance plans with colonoscopy!

\(^2\) Stein AC, Rubin DT. ACG 2012, poster P379.

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
  - 5 Years

- Intermediate Risk
  - Extensive colitis with MILD ACTIVE endoscopic/histological inflammation
  - OR post-inflammatory polyps
  - OR family history CRC in FDR aged 50+
  - 3 Years

- 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
  - 1 Year

Biopsy Protocol
Pancolonic dye spraying with targeted biopsy of abnormal areas is recommended, otherwise 2–4 random biopsies from every 10 cm of the colorectum should be taken.

Other Considerations
Patient preference, multiple post-inflammation polyps, age and comorbidity, accuracy and completeness of examination.
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5-year interval

3-year interval

1-year interval

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Summary: Prevention of Colorectal Cancer in IBD

- The risk of CRC in IBD is less than previously thought. This may be from effective therapies (surgical and medical), effective prevention (!) or from more accurate studies.

- Degree of inflammation is a significant risk factor for CRC in UC. Stratifying intervals for surveillance is one way to incorporate this into practice.

- Improving our ability to identify dysplasia changes the predictive value of such lesions.

- We are moving towards “smart prevention” using a model of compounded risks in individual patients.