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IBD and Colon Cancer Surveillance

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Disclosures:
Speaker’s Bureau: Abbott, Janssen, Santarus
Research: CDC/NIH/CCFA
OSCCAR

Thx: Francis Farraye, MD

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Goals
- Increased risk of colon cancer in IBD
- Importance of surveillance/technique
- Consider Chromoendoscopy
- Suggested Guidelines (evolving)
- Confirmed dysplasia = colectomy
  - HGD/DALM
  - LGD* controversial

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The Enemy: Colorectal Cancer

The risk of colorectal cancer in IBD is nearly 20 times higher than the general population
Cancer and IBD

- Increased risk of colorectal cancer in UC\(^1,2\)
  - 0.5-1.0% per year after first decade of disease
  - 2% at 10 years, 8% at 20 years, 18% at 30 years
- Risk is equivalent for UC and CD
  - Duration
  - Extent
- Cancers occur earlier in these patients
- Dysplasia in flat mucosa
- Risk not increased in patients with proctitis

\(^1\)Ransohoff. Gastroenterology 1988;94:1089
\(^2\)Eaden et al. Am J Gastro 2000;95:2710

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Is the Risk This High?

- 600 patients with extensive UC followed for 5932 person-years at St. Marks in London
- 30 CRCs detected (annual risk: 0.5% or 1/200)
- Cumulative probability of CRC was 2.5% at 20 years, 7.6% at 30 years and 10.8% at 40 years
- Linear regression suggested that CRC risk declined over the course of the study


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Cumulative Risk of Colorectal Cancer in UC

Eaden JA. Gut 2001; 48:525-35

Proximal
Distal

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COLORECTAL CANCER RISK IN ULCERATIVE AND CROHN’S COLITIS

Risk of GI Cancer in IBD

Bernstein CN. Cancer 2001; 91:854-62
Cancer Risk Factors in IBD

- Extensive disease
  - Higher risk: pancolitis
  - Lower risk: proctosigmoiditis
- Disease duration
- Family history of colorectal cancer
- Primary sclerosing cholangitis
- Histologic Disease activity
  (severity of inflammation)
- Probable risk factors
  - Folate deficiency
  - Poor compliance with medical therapy

Rutter, et al. Gastroenterology, 2004

Cancer Surveillance in Colitis

Inflammation  Dysplasia  Cancer  Death

Intervene screening and surveillance
Intervention to prevent further progression: surgery

Dysplasia in IBD

- Unequivocal neoplastic epithelium confined to the gland in which it arose
- Marker of malignancy risk
- Present in 75-80% (close and distant) of patients with carcinomas
- Any portion of colon (parallels cancer)
  - single, multifocal, diffuse
- Flat or elevated (DALM)
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**Dysplasia Classification**

- Negative for dysplasia
- Indefinite for dysplasia (probably negative, unknown and probably positive)
- Positive for low-grade dysplasia, high-grade dysplasia or invasive cancer
- Pathologists should no longer be grading dysplasia as mild, moderate or severe


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**Limitations of Using Dysplasia as Endpoint**

- Interobserver variation
  - Several studies demonstrated only moderate levels of agreement
  - Agreement better for HGD/Negative than LGD/Indefinite
  - Confirm diagnosis by expert GI pathologist
- Scope when IBD quiescent
- Need for patient compliance with colonoscopy
- Dysplasia may be absent in 25-30% of colectomy specimens in patients with cancer

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**Interobserver Variation in Diagnosis of Dysplasia**

<table>
<thead>
<tr>
<th>Degree of Dysplasia</th>
<th>% Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Grade</td>
<td>77</td>
</tr>
<tr>
<td>Low Grade</td>
<td>63</td>
</tr>
<tr>
<td>Indefinite</td>
<td>49</td>
</tr>
<tr>
<td>Negative</td>
<td>74</td>
</tr>
</tbody>
</table>

Colonoscopic Surveillance for UC

- Can detect UC cancers at a curable stage for many patients
- Cancer mortality is reduced with surveillance
  - 77% vs 37% 5 year survival
- At initial screening, 3% will have cancer and 11% will have dysplasia


Mortality Benefit from Surveillance in UC

- Lahey Clinic Study 1974-1991, 2050 pts
- 19 cancers in surveillance group
  - Duke’s A (7) B (8) C (4)
  - 5-yr survival 77.2%
- 22 cancers in nonsurveillance group
  - Duke’s A (3) B (6) C (13)
  - 5-yr survival 36.3%

\[ \text{P} = 0.026 \]

CRC and UC Surveillance Colonoscopy

- Retrospective
- Case control Study
- UC + CRC
  - 40 patients
- UC no CRC
  - 102 patients

Karlen P. Gut 1998; 42: 711-14
**Surveillance in chronic UC**

**My Guidelines**

- Colonoscopic surveillance
  - after 8-10 years of disease in patients with pan colitis
  - after 12-15 years in patients with left sided disease
- Q1-3 years
  - Consider FH, PSC, age, symptoms etc.
- After 20 years, annual colonoscopy
- NNT = 14 to prevent 1 cancer; 40 to prevent 1 death


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**Suggested Intervals for Surveillance Colonoscopy**

- Screening Colonoscopy (at 8-10 yr of disease)
  - Dysplasia:
    - Repeat q 2-3 yrs
    - No Dysplasia
      - Repeat q 1-2 yrs

Note: Patients greater than age 50 need screening for polyps and adjust schedule according to symptoms (bleeding).

*Follow dysplasia algorithm.*

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**Colorectal Cancer in Ulcerative Colitis**

**DYSPLASIA**

- Inflammatory Change
- Dysplasia
- Surveillance best during remission
SURVEILLANCE BIOPSY PROTOCOL

SURVEILLANCE FOR DYSPLASIA IN UC
- >32 biopsies are needed to exclude dysplasia with 90% confidence
- 4 quadrant biopsies every 10 cms
- Additional biopsies - suspicious mucosal lesions
- Disease in remission at time of colonoscopy
- Surveillance is not perfect
- Prophylactic colectomy an option

Levin B. ASGE Clinical Update 2000;7:1313-6

SURVEYING SURVEILLANCE:
What are we (not) doing?
- 79% of physicians biopsy 2-4 sites
- 54% biopsy 5-9 sites
- 36% biopsy 10 or more sites
- Confusion about dysplasia, DALM

Dysplasia Associated Lesion Mass (DALM)

"DALM" coined by Blackstone et al. Gastroenterology, 1981;80:366-74

Dysplasia in IBD

Gross Subtypes
- Flat
- Elevated (DALM)
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**Confirmed Dysplasia in CUC**

- Flat
  - low grade*
  - high grade*
  - low/high grade*

- DALM
  - colectomy

*confirmation by 2nd expert pathologist
#controversial, though most (including me!) recommend colectomy

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**Colectomy for Dysplasia in UC**

- Low grade dysplasia → 20% cancer
- High grade dysplasia → 42% cancer
- DALM → 43% cancer
- The finding of dysplasia of any grade should be confirmed by a pathologist with special expertise in gastrointestinal pathology
- **Confirmed dysplasia = colectomy**

Bernstein et al, Lancet 1994;334:71

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**The fate of low grade dysplasia**

- Mt Sinai: 46pts → LGD on chart review
  - 7 cases of CRC
  - 4/17 (23.5%) had unexpected CRC at colectomy
  - 53% progression to advanced neoplasia at 5yr
  - 2 cancers at advanced stage despite surveillance
  - Unifocal LGD same risk as multifocal or recurrent LGD
- **Confirmed LGD = Colectomy**

Ullman, et al., Gastroenterology 2003;125:1311-1319
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The fate of low grade dysplasia

![Graph showing progression over time](image)

Ullman T Gastro 2003; 125:1311-19

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Dysplasia Surveillance in UC: Recommended Actions

- Indefinite findings: increase surveillance
- Negative findings: survey according to duration and other RF
  - >8 years: every 1-3 years
  - >20 years: every year
- DALM, high grade, low grade: colectomy


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Confirmed Dysplasia by 2 expert pathologist = COLECTOMY in UC
Controlled Studies on the Use of Chromoendoscopy in UC

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Dye</th>
<th>Difference (x-fold)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiesslich et al. (2003)</td>
<td>165</td>
<td>MB</td>
<td>10 (32 vs 10)</td>
<td>3.07</td>
</tr>
<tr>
<td>Hurlstone et al. (2004)</td>
<td>324</td>
<td>IC and magnification</td>
<td>69 (69 vs 24)</td>
<td>3.81</td>
</tr>
<tr>
<td>Rutter et al. (2004)</td>
<td>100</td>
<td>IC</td>
<td>7 (7 vs 0)</td>
<td>4.50</td>
</tr>
<tr>
<td>Kiesslich et al. (2007)</td>
<td>153</td>
<td>MB and Confocal Endomicroscopy</td>
<td>23 (19 vs 4)</td>
<td>4.75</td>
</tr>
<tr>
<td>Marion et al. (2008)</td>
<td>102</td>
<td>MB</td>
<td>17 (17 vs 9)</td>
<td>5.66</td>
</tr>
</tbody>
</table>


Pit Pattern Classification (Kudo)

The typical crypt architecture of types I-V are indicated (A). (B) Examples of type I (left) and type IV (right) lesions before and after chromoendoscopy.

Chromoendoscopy: Which Dye?

- **Indigo carmine (0.1%-0.4%)**
  - Contrast stain neither reacts or is absorbed by the colonic mucosa
  - Pools in mucosal grooves allowing better definition of small or flat lesions as well as alterations in mucosal architecture
  - Can be washed off the mucosa

- **Methylene blue**
  - Vital dye taken up by colonic mucosa within 1-2 minutes staining noninflamed mucosa but is poorly taken up by dysplastic tissue or inflamed mucosa

- **No published studies comparing indigo carmine to methylene blue in patients with IBD**

Chromoendoscopy in practice

- Single physician experience 2005-8/2012
- 184 scopes; 118 pts, mean age 51.4 years

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Chromo-IC (64 scopes)</th>
<th>WLE (120 scopes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>38.5 minutes</td>
<td>20.5 minutes</td>
</tr>
<tr>
<td>Biopsies</td>
<td>42.0 bx (13 jars)</td>
<td>33.8 bx (10 jars)</td>
</tr>
<tr>
<td>Polyps</td>
<td>157 polyps (2.45/scope)</td>
<td>87 polyps (0.725/scope)</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>25/64 (39.1%) dys polyps</td>
<td>8/120 (6.9%) dys polyps (p&lt;0.001)</td>
</tr>
</tbody>
</table>

*Flat dysplasia on one random biopsy

Jatsukar N, Reinert S, Resnick M, Shah S

The Future of Endoscopic Imaging in Patients with IBD


Goals

- Increased risk of colon cancer in IBD
- Importance of surveillance technique
- Consider Chromoendoscopy
- Suggested Guidelines (evolving)
- Confirmed dysplasia* = colectomy
- YOU CAN HELP:
  - Is the pt due for colonoscopy
  - # biopsies, careful technique, Chromo
Future

- Chromoendoscopy with only targeted biopsies; longer intervals in between scopes
  - Random biopsies yield is very low
  - Biopsies adds time and cost
- Stool DNA
- Blood tests to detect presence of dysplastic tissue in colon
- Chemoprevention: 5-ASA, Urso, Folic acid
  - Future: ?

Should colectomy be performed for flat dysplasia?

- Grade A: There is high certainty that colectomy for flat HGD treats undiagnosed synchronous cancer and prevents metachronous cancer.
- Grade Insufficient: The current evidence is insufficient to assess the balance of benefits and harms of colectomy for flat LGD.


IBD Patient with Flat Dysplasia

High grade

- Colectomy or Increase Surveillance

Low grade

- Multifocal Colectomy
- Unifocal Colectomy

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DALMs (Polypoid or Raised Dysplasia)

Adenoma-like
Endoscopically resectable

Non-adenoma-like
Non-endoscopically resectable

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Long term Followup of Polypoid Dysplasia Resected Endoscopically

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No further polyps</td>
<td>38%</td>
<td>52%</td>
</tr>
<tr>
<td>Additional polyps</td>
<td>58%</td>
<td>48%</td>
</tr>
<tr>
<td>Dysplasia in flat mucosa</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>CRC</td>
<td>4%</td>
<td>0%</td>
</tr>
</tbody>
</table>


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DALMs (Polypoid or Raised Dysplasia)

Adenoma-like
Endoscopically resectable

Outside colitis
Polyectomy
Regular surveillance

Inside colitis
Polyectomy
Absence of flat dysplasia
? Increase surveillance

Non-Adenoma-like
Non-endoscopically resectable

Colectomy
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**Polyps in IBD: Pseudopolyp (PP), Adenoma like DLM (ALD) or Non Adenoma Like DLM (NALD)**


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**Endoscopist’s Nightmare**

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**Is there sufficient rationale for performing surveillance colonoscopy in patients with IBD?**

Grade B: There is moderate certainty that surveillance colonoscopy results in at least moderate reduction of CRC risk in patients with IBD.

- Despite the lack of randomized controlled trials, surveillance colonoscopy is recommended for patients with IBD at increased risk for developing CRC.
- Patients with extensive UC or CD of the colon are most likely to benefit from surveillance.

Surveillance Colonoscopy

- All patients should undergo a screening colonoscopy a maximum of 8 years after onset of symptoms
- Regardless of extent of disease at diagnosis
- Multiple biopsies to assess microscopic extent of inflammation
- Ulcerative proctitis or proctosigmoiditis are not considered at increased risk for IBD-related CRC
- Manage on the basis of average-risk recommendations
- Patients with extensive or left-sided colitis should begin surveillance within 1 to 2 years after the initial screening colonoscopy


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Surveillance Colonoscopy

- The optimal surveillance interval has not been clearly defined
- After 2 negative examinations survey every 1 to 3 years
- Representative biopsy specimens from each anatomic section of the colon should be obtained
- Minimum of 33 biopsy specimens to be taken in pancolitis patients
- Chromoendoscopy with targeted biopsies is recommended as an alternative to random biopsies for endoscopists who have expertise with this technique
- Increased sensitivity for detecting dysplasia


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Surveillance Colonoscopy

- Patient with PSC
  - Survey at time of diagnosis and then yearly
  - Ideally, surveillance colonoscopy should be performed when the colonic disease is in remission
  - More frequent surveillance examinations:
    - History of CRC in first-degree relatives
    - Ongoing active endoscopic or histologic inflammation
    - Anatomic abnormalities such as a foreshortened colon, stricture
    - Multiple inflammatory pseudopolyps
  - Same recommendations for patients with Crohn’s colitis who have disease involving at least one third of the length of the colon
