Surveillance Colonoscopy for Dysplasia and Cancer in Children and Young Adults with Colonic IBD

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Are children with colitis at risk for colorectal cancer?
Who do we have to screen?
- Ulcerative colitis?
- Proctosigmoiditis?
- Crohn’s colitis?

Disclosures
- Consultant
  - Janssen Pharmaceuticals
  - UCB

CRC Risk in Childhood Onset UC
- Mayo Clinic 1919 - 1965
- 396 children age <14 yrs at Dx of UC
- Ca Risk = 20% per decade after first decade of UC
- Cumulative incidence of Ca at 35 yrs of UC = 43%

Cumulative Risk of Developing Colorectal Cancer in Any Patient with UC
- Meta-analysis
  - 116 studies
  - >50,000 pts
- After 10 yrs, CRC rate increases ~0.5-1% per yr

Cumulative Probability of CRC Risk: Childhood vs Adult Onset UC
- Extent of pancolitis
  - Adults: ~20%
  - Children: ~50%

**Cumulative Probability of CRC Risk: Childhood vs Adult Onset UC**

- **Children:**
  - 0% after 10 yrs
  - 2% after 20 yrs
  - 4% after 30 yrs
- **Adults:**
  - 2% after 10 yrs
  - 4% after 20 yrs
  - 6% after 30 yrs

**Risk of CRC in Childhood Onset UC**

- **Population-based study from Sweden, 1922-1984**
- **3117 patients**
  - 266 diagnosed <15 years of age
  - 19% proctitis, 24% left sided UC, 56% pancolitis

<table>
<thead>
<tr>
<th>Extent of Colitis</th>
<th>Observed Cases</th>
<th>Person Years of Follow-up</th>
<th>Std Incidence Ratio (95% Confidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left sided</td>
<td>0</td>
<td>1967</td>
<td>0 (0-173)</td>
</tr>
<tr>
<td>Pancolitis</td>
<td>13</td>
<td>2525</td>
<td>162 (86-277)</td>
</tr>
</tbody>
</table>

**Cumulative incidence of cancer at 35 yrs of UC = 40%**

-Ekbom, et al. NEJM 1990;323:1228-33

**Proctosigmoiditis in Children**

- **An uncommon diagnosis in children**
  - Peds IBD Registry: 81% with pancolitis at Dx
- **Proximal extension to left sided or extensive colitis common:**
  - Mir-Madjelessi: 38/66 (58%) within 5 yrs
  - Hyams: 11/38 (29%) in median 2.6 yrs

- Hyams J et al. Am J Gastroenterol 2011 (advanced online publication)

**Colitis in young children often turns out to be Crohn’s Disease**

- **At Dx,** isolated colonic disease noted in:
  - 63% children < 8 yrs of age
  - 35% children ≥ 8 yrs of age
- **In children <5 yrs at Dx of UC or IBD-U:**
  - 11/55 (20%) ultimately proven to have Crohn’s disease


**Risk of Dysplasia or Cancer in Pancolitis**

- **Single center database (Paris)**
- **Dx’d 1974-2002,** followed to 2010
- **Subjects:** 523 (CD), 276 (UC), 56 (IBD-U)
- **N = 75** (neoplasia)

- **25 yr cumulative risk for advanced HGD or CRC**
  - UC + IBD-U: 29.5 ± 5.7%
  - All CD: 3.9 ± 2.0%
  - “UC-like” CD: 10.6 ± 7.2%


**Risk Factors for CRC In Colitis**

- **Primary Risk Factors**
  - Extent of disease
  - Duration of disease
- **Protective Factors**
  - ? SASA treatment
  - ? Thiopurine Rx

- **Secondary Risk Factors**
  - Age at onset of colitis
  - Family history of colon cancer
  - Sclerosing cholangitis
  - Chronically active disease
- **Not Risk Factors**
  - Intensity of first attack
  - Severity of colitis
  - Immunosuppressive Rx
Screening vs Surveillance

- Screening colonoscopy
  - Generally started 8-10 yrs after initial dx
  - Determine extent of colitis
  - Evaluate for dysplasia or cancer
- Surveillance
  - Regularly scheduled colonoscopies designed to identify newly developed dysplasia or cancer

What is the optimal method for performing dysplasia surveillance?

1. Pancolonoscopy with random 4 quadrant biopsies every 10 cm
2. Pancolonoscopy with targeted biopsies

Random biopsy protocol

- Standard white light colonoscopy
- Random 4 quadrant bx q10 cm from cecum to rectum
- Requires:
  - 33 bx to r/o dysplasia with 90% certainty
  - 56-64 bx to r/o dysplasia with 95% certainty
- Protocol derived from sampling of colectomy specimens
- Identifies large areas of dysplasia for which risk of progression to cancer is fairly well established

Targeted biopsy protocols

- Utilize new endoscopic techniques to direct biopsies to areas of high risk
  - Chromoendoscopy with dye spray
  - Narrow band imaging
  - Magnification endoscopy
  - Confocal endomicroscopy
- Identify small fields of dysplasia
  - Progression to cancer less well established

Chromoendoscopy

- Utilize new endoscopic techniques to direct biopsies to areas of high risk
- Chromoendoscopy: Pit Patterns
- Dye spray catheter
- Mucosa stained with methylene blue
- Magnifying analysis and pit pattern

Rubin CE et al. Gastroenterol 1992;103:1611-1620

Kiesslich R and Neurath M. Gastroenterol Clin N Am 2012;41:291-302

Chromoendoscopy: Pit Patterns

http://www.humira.no/Picture-IT/Gastroenterology/Endoscopy/Chromoendoscopy.aspx
Chromoendoscopy Improves Dysplasia Yield

<table>
<thead>
<tr>
<th></th>
<th>Random</th>
<th>Non-Dye Targeted</th>
<th>Dye Targeted</th>
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<tbody>
<tr>
<td>LGD or HGD</td>
<td>3/3264 (0.09%)</td>
<td>13/50 (26%)</td>
<td>22/82 (27%)</td>
</tr>
</tbody>
</table>

Marion J et al. Am J Gastroenterol 2008;103:2342–2349

Guidelines for Chromoendoscopy

- Evaluate patients in clinical remission (avoid active disease)
- Excellent bowel prep!
- Intubate to the cecum, examine on withdrawal
- Panchromoendoscopy (not local staining)
  - 0.4% indigo carmine or 0.1% methylene blue
  - Use dye-spray catheter to improve mucosal coverage
  - Apply to 20-30 cm length segments and examine carefully
- Analyze the pit pattern
  - Types I–II suggest nonmalignant lesions
  - Types III–V suggest intraepithelial neoplasia and carcinomas
- Perform targeted biopsies of all mucosal alterations, esp:
  - circumscribed lesions
  - lesions with pit patterns III–V

Modified from Kiesslich R and Neurath M. Gastroenterol Clin N Am 2012;41:291–302

Narrow Band Imaging: “Virtual Chromoendoscopy”

- Uses optical filters to illuminate mucosa with light narrowed to the wavelength maximally absorbed by hemoglobin
- Accentuates mucosal and submucosal vessels
- May delineate extent of lesions better than white light endoscopy
- Image similar to that seen with chromoendoscopy

Narrow Band Imaging: No Better than Standard or High Definition Endoscopy

- 42 adults with surveillance by both NBI and conventional colonoscopy within 3 weeks
  - 11 patients with neoplasia
  - 4 NBI only, 3 conventional only, 4 both

- 48 adults underwent surveillance by both NBI and high definition colonoscopy within 3 weeks
  - 16 neoplastic lesions in 11 patients identified
  - Patients: 9/11 identified by HDE, 8/11 by NBI
  - Lesions: 11 (69%) by HDE, 13 (81%) by NBI, p=0.727


NBI – No Better than High Def White Light Endoscopy

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<thead>
<tr>
<th></th>
<th>NBI</th>
<th>WLE</th>
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<tbody>
<tr>
<td># subjects with dysplasia</td>
<td>5/56</td>
<td>5/56</td>
</tr>
<tr>
<td># true dysplastic lesions by targeted bx</td>
<td>5/17 (29%)</td>
<td>7/11 (64%)</td>
</tr>
<tr>
<td>Overall rate of dysplasia by random 4 quadrant bx q10 cm:</td>
<td>1/2707 (0.04%)</td>
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Confocal Endomicroscopy
- In vivo microscopic examination of the mucosa during endoscopy
  - Requires another modality (e.g., NBI, chromoendoscopy) to identify targeted areas for exam
  - Requires fluorescent contrast agent to achieve high-contrast images


Endomicroscopy
- Advantages
  - Real-time pathological assessment
  - No biopsy required
  - Eliminates need for and expense of pathologist
- Disadvantages
  - Eliminates need for pathologist
  - Endoscopist now also pathologist → enhanced training, interobserver variability

Newer Techniques: “Optical Biopsy”
- Allow machine-based assessments
  - More objective and less operator dependent than visual interpretation
- Spectroscopic analyses
  - In situ, real-time measurements
  - Measure spectral signatures of light scattered by subcellular components of tissue
  - Not an imaging technique; semi-quantitative, algorithm driven

Optical Coherence Tomography
- Adenoma
- Healthy tissue

Laser Induced Fluorescence
- Mouse colon

Optical forceps

Optimal Intervals for Surveillance
- No controlled trials
- Guidelines based on clinical experience and published surveillance observations

AGA 2010
- Screening after 8 yrs for all UC; at Dx for PSC
- Surveillance q1-3 yrs for extensive and left sided colitis; q1 yr for PSC
- Random bx protocol
- Colectomy for HGD in flat mucosa; data insufficient for LGD

Farray F et al. Gastro 2010;138:738–745

ACG 2010
- Screening after 8-10 yrs for all UC; at Dx for PSC
- Surveillance q1-2 yrs for extensive and left sided colitis; q1 yr for PSC
- Random bx protocol
- Colectomy for HGD in flat mucosa; also for LGD