Colorectal cancer screening in Inflammatory Bowel Disease: The role of Chromoendoscopy
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University of Wisconsin.

Objectives

- Identify high risk patients by understanding the risk factors for developing colorectal neoplasia in IBD
- Contrast random vs. targeted biopsies
- Discuss evidence for chromoendoscopy in IBD
- Review how to incorporate chromoendoscopy in your clinical practice.

Case

- 56yo with 20 year hx of Crohn's Colitis is referred for 2nd opinion due to cecal biopsies with low grade dysplasia.
- Next step?
- A) Refer for colorectal surgery
- B) Repeat Colonoscopy with random Biopsies using new HD scope with NBI
- C) second opinion from pathology
- D) Repeat Colonoscopy with Chromoendoscopy
My previous approach to Chromoendoscopy

- **WHO:**
  - Pancolonic: High risk (PSC, previous confirmed dysplasia)
  - Long term pancolonic UC
- **PREP:** needs to be clean and in remission
- **HOW:** methylene blue power wash
Cumulative risk of developing CRC in UC Historical Meta-analysis

![Cumulative risk graph]

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Risk of CRC in IBD is elevated

Inflammation of the colon is the key factor

<table>
<thead>
<tr>
<th>Site</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All CD</td>
<td>2.5</td>
<td>1.3-4.7</td>
</tr>
<tr>
<td>Colon</td>
<td>4.5</td>
<td>1.3-14.9</td>
</tr>
<tr>
<td>Ileum</td>
<td>1.1</td>
<td>0.8-1.5</td>
</tr>
</tbody>
</table>

Canavan C et. al. Aliment Pharmacol Ther 2005

Risk of Colorectal Cancer in Patients with UC
Recent Meta-analysis

<table>
<thead>
<tr>
<th>Risk of colorectal cancer in ulcerative colitis</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steiger et al. Stockholm, 1986-1996</td>
<td>2.1 (0.5, 4.1)</td>
</tr>
<tr>
<td>Wrincher et al. Denmark, 1963-1987</td>
<td>1.08 (0.56, 1.70)</td>
</tr>
<tr>
<td>Hall et al. Italy, 1978-1987</td>
<td>1.79 (0.95, 3.36)</td>
</tr>
<tr>
<td>Standeven et al. Canada, 1988-1991</td>
<td>3.16 (0.88, 11.00)</td>
</tr>
<tr>
<td>Wendel et al. Denmark, 1973-1998</td>
<td>1.67 (0.91, 3.00)</td>
</tr>
<tr>
<td>Jess et al. USA, 1993-2001</td>
<td>1.13 (0.74, 1.74)</td>
</tr>
<tr>
<td>Jess et al. Denmark, 1993-2002</td>
<td>3.16 (1.71, 5.70)</td>
</tr>
<tr>
<td>Sønderby et al. Denmark, 1954-2004</td>
<td>2.71 (1.33, 5.52)</td>
</tr>
<tr>
<td>Pooled estimate, random effects</td>
<td>2.08 (0.55, 8.27)</td>
</tr>
</tbody>
</table>


Selby Inflamm Bowel Dis. 2008:14:253-58
Cumulative Risk of Colorectal Cancer in IBD
Referral Center v. Population Based Studies

- Meta analysis of cohort studies reporting occurrence of CRC in recent population-based studies
- 323,536 person years
- Overall cumulative risk at 10, 20 and 20+ years is 1%, 3% and 7%
- Rate higher in referral centers and those with extensive disease

Factors That Increase the Risk of CRC in IBD

- Duration of colitis
  - Increases after 10 years
- Anatomic extent of disease
  - 15 x greater in pancolitis
  - No increase in proctitis patients, intermediate risk in left sided UC and highest risk in pancolitis
- Primary sclerosing cholangitis
  - 5 x greater
- Family history of colorectal cancer
  - Highest risk if FDR with CRC <50 (2.5 greater)
- Age of IBD onset

Selby Inflamm Bowel Dis. 2008:14:253-58
Factors that Increase the Risk of CRC in IBD

- Previous dysplasia
- Endoscopic findings
  - Strictures, pseudopolyps
- Male Gender

Endoscopic Predictors of CRC Risk in UC

- Case Control study (1988 through 2002) of patients with CRC (n=68) and controls (n=136)
- Multivariate Analysis
  - Macroscopically normal colon (OR 0.38; CI, .21-.74)
  - Post Inflammatory polyps (OR 2.29; CI 1.28-4.11)
  - Strictures (OR 4.62; 1.03-20.8)
- Five year risk of CRC following a normal colonoscopy was no different than that of matched general populations

Only one risk factor is modifiable

- Potentially modifiable risk factor:
  - Histologic inflammation at surveillance colonoscopy

Selby Inflamm Bowel Dis. 2008:14:253-58
Why might IBD related colorectal cancer incidence be decreasing?

- Primary prevention
  - Medications/control inflammation
  - Earlier surgery in medical refractory cases
  - IPAA for ulcerative colitis more attractive than ileostomy
- Secondary prevention
  - Identification of dysplasia and colectomy
  - Identification of dysplasia and polypectomy

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20th Century Cancer Surveillance in IBD Colitis

- Inflammation
- Dysplasia
- Cancer

- Initiate screening and surveillance
- Intervention to prevent further progression: surgery

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21st Century Cancer Surveillance in IBD Colitis

- Inflammation
- Dysplasia
- Cancer

- Initiate screening and surveillance
- Intervention to prevent further progression: surgery & polypectomy

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Who should get surveillance?

- All patients with ulcerative colitis and Crohn’s colitis should undergo a screening colonoscopy 8-10 years after onset of disease symptoms to stage extent (histologically) of disease and evaluate for an increased risk for IBD associated colorectal neoplasia.

- Surveillance colonoscopy
  - Ulcerative colitis patient with left sided or extensive colitis (excluding patients with isolated proctitis)
  - Crohn’s colitis patients involving more than one segment of the colon or at least 1/3 of the colon.

Surveillance Technique

- Based on expert opinion
  - Based on initial that dysplasia occur in flat mucosa and as a widespread “field effect”

- Technique: 4-quadrant biopsies every 10 cm of mucosa; at least 33 biopsies; extra focus on nodules, masses, strictures; every 5 cm in rectosigmoid

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.
Better survival from CRC in patients undergoing surveillance

- 149 patients with IBD associated CRC from the Netherlands (1/90 to 7/06)
- 100% five year survival of 23 patients enrolled in a surveillance program prior to CRC detection compared to 74% in a non-surveillance group (P=0.042)
- 52% of patient in the surveillance had Stage 0-1 CRC compared to 24% in the non-surveillance group (P=0.004)

Lutgers et al.: Colonoscopic surveillance improves survival after colorectal cancer diagnosis in IBD. Br J Cancer 2009;101:1671-5

Most recent GI society surveillance guidelines

How to choose?

<table>
<thead>
<tr>
<th>Society</th>
<th>First colonoscopy (Screening)</th>
<th>Subsequent colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCCN (2004) and ADF (2007)</td>
<td>All patients 8-10 years after diagnosis</td>
<td>Every 3 years</td>
</tr>
<tr>
<td>DFD's and Cooke Foundation (2004)</td>
<td>All patients 8-10 years after diagnosis</td>
<td>Every 2 years: ( T \leq 2 \times 1 \times 3 ) years then every 1-2 years until disease diagnosed: 2 years in PSC</td>
</tr>
<tr>
<td>ASGE (2010)</td>
<td>All patients 8 years after symptom onset (except patients with pancolitis)</td>
<td>Every 5 years after screening: Every 5 years after 2 negative examinations</td>
</tr>
<tr>
<td>British Society Gastroenterology (2009)</td>
<td>All patients 10 years after diagnosis to determine extent and endoscopic risk factors</td>
<td>Yearly in patients with active/mild inflammation or stricture or PSC or history of dysplasia or FNH age &lt; 50 yrs. Every 5 years in patients with mild inflammation or inflammatory polyps or FNH age &gt;50 yrs. Every 5 years in patients with quiescent colitis or left sided colitis</td>
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British Society Guidelines 2010

Lower Risk: Patients with inactive/Clinically stable disease and no history of dysplasia or CRC

Intermediate Risk: Patients with prior dysplasia or CRC

Higher Risk: Patients with prior dysplasia or CRC and current dysplasia or active inflammation

2 Year Screening

3 Year Screening

5 Year Screening

FBR: Farnesyl transferase inhibitors, PPI: proton pump inhibitors, IBD: inflammatory bowel disease, CRC: colorectal cancer, PSC: primary sclerosing cholangitis, FH: family history, FNH: familial adenomatous polyposis

Selby Inflamm Bowel Dis. 2008:14:253-58
Limitations of random biopsies

- Surface area of colorectum: 15781 +/- 301.0 cm²
- Surface of area of biopsy forceps 2.2-5mm
- With 33 biopsies
- Sample 0.05-0.1% of colon surface
- To detect a 2cm patch of dysplasia within the colon would need around 320 specimens.

Low yield of Random Biopsies in Colitis Surveillance

- Random Biopsies¹
  - N = 167 patients, 466 surveillance colonoscopies
  - 24 of 11,772 random biopsies detected neoplasia (0.2% - per biopsy yield
  - Only in 5 colonoscopies involving 4 patients
  - 1 in 500 random biopsies

Yield of dysplasia from Random Biopsies in studies

<table>
<thead>
<tr>
<th>Study Author, Year</th>
<th>Image Enhancement Modality</th>
<th>Number of patients</th>
<th>Number of Random Biopsies with Dysplasia</th>
<th>Total Number of Random Biopsies</th>
<th>Mean number of random biopsies per episode of dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiesslich et al, 2003</td>
<td>Methylene blue chromoendoscopy</td>
<td>165</td>
<td>2 (in white light arm only)</td>
<td>5098</td>
<td>2556</td>
</tr>
<tr>
<td>Matsumoto et al, 2003</td>
<td>Indigo carmine chromoendoscopy</td>
<td>57</td>
<td>0</td>
<td>792</td>
<td>204</td>
</tr>
<tr>
<td>Nierhoff et al, 2006</td>
<td>Indigo carmine chromoendoscopy</td>
<td>100</td>
<td>0</td>
<td>2904</td>
<td>0</td>
</tr>
<tr>
<td>Kiesslich et al, 2007</td>
<td>Methylene blue chromoendoscopy</td>
<td>115</td>
<td>2 (in white light arm only)</td>
<td>2862</td>
<td>1328</td>
</tr>
<tr>
<td>Marion et al, 2008</td>
<td>Methylene blue chromoendoscopy</td>
<td>42</td>
<td>0</td>
<td>1044</td>
<td>250</td>
</tr>
</tbody>
</table>
Poor adherence to protocol

- British survey of Gastroenterologist
  - 57% took fewer than 10 biopsies
  - 2% took more than 20
- Another survey revealed
  - 54% of gastroenterologists reported obtaining at least 31 biopsy
- Retrospective study
  - only 18% of surveillance examinations in subjects with extensive colitis yielded 20 or more mucosal biopsy specimens


Most dysplasia is Visible with White Light

- St Marks Group 1988-2002 Retrospective review of neoplasia
  - 525 patients, 2204 surveillance exams
  - Random biopsies “non-targeted” as well as “targeted” biopsies of macroscopic lesions
  - 110 dysplastic lesions in 56 patients
  - In 89% of patient in whom dysplasia found, visible to the endoscopist.

Most dysplasia is Visible with White Light

- 1339 exams, 622 patients surveillance colonoscopies with chronic UC
  - 1994-2002 University of Chicago
  - Targeted and non-targeted biopsies
  - 73 dysplastic lesions in 46 patients
  - In 78% of patient dysplasia visible to endoscopist.

Interval CRC Highest in IBD

- SEER registry 55,000 Medicare patients
- Rates of early/missed CRC 3 greater in IBD vs. non IBD
- 15.1% Crohns
- 15.8 for UC
- 5.8 for non IBD
- CRC within 6 to 36 months after colonoscopy exam

Want YR. Am J gastro 2013
Pathologist cannot decide importance of dysplasia is given by endoscopic context
- Tubular adenoma= low-grade dysplasia

Confusing terminology for dysplasia in IBD
- DALM (dysplasia associated lesion or mass)
- Adenoma like (endoscopically respectable)
- Non-adenoma like
- “Flat”
- Visible (DALM)dysplasia “Invisible dysplasia”

Better:
- How detected (Non-targeted vs. targeted biopsies)
- Can borders be defined

Proposed Classification to IBD Related Dysplasia
Macroscopic Classification of Superficial Colorectal Neoplasia (Type 0)
- Type 0-I (Polyoid or P-CRN)
- Type 0-II (Nonpolyoid or NP-CRN)

Source: Gastrointestinal Endoscopy Clinics of North America 2014; 24:483-520 (DOI:10.1016/j.giec.2014.04.003)
Chromoendoscopy proposed as means of improving sensitivity of colonoscopy

- Spraying of dye in the colon
- Two main uses in IBD
  - Surveillance
  - Improve detection of subtle colonic lesions (increase sensitivity of surveillance)
  - Once lesion detected to aid in differentiating between neoplastic and non-neoplastic based on crypt architecture and modified pit pattern

Significance of Pit Patterns

Type I/II predict non-neoplastic lesions

Type III/IV/V predict neoplastic lesions

Kudo S et al. Endoscopy 1993

Source: Gastrointestinal Endoscopy Clinics of North America 2014; 24:483-520 (DOI:10.1016/j.giec.2014.04.003)
Non-polypoid Colorectal Neoplasm Common in IBD

- 63 patients with inactive UC for more than 10 years
- 23 neoplasms, 67% flat
- 3 HNPCC (1 flat and 1 sessile)

Difference Between Chromoendoscopy and Virtual chromoendoscopy

- **Chromoendoscopy**
  - Dye spray through catheter
  - Absorptive dye: (stain taken up by noninflamed mucosa but poorly taken up by active inflammation and dysplasia): methylene blue
  - Contrast dye (coats surface to highlight subtle disruptions of normal contours): indigo carmine

- **Virtual chromoendoscopy**
  - Rotating color filters the R-G-B bands while increasing the relative intensity of blue bands
  - Post-processing techniques (i-Scan/Fujinon) to achieve pseudocolored image
  - Enhance tissue vasculature (differential optical absorption of light by Hb associated with dysplasia (blue band)) or mucosal contours
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
  - Taken up by colonic mucosa within 1-2 minutes staining noninflammed 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

Landmark study

- 2003 Kiesslich et al RCT of 165 UC patients 1:1 Chromoendoscopy CE vs White light (WL)
  - CE detect more dysplasia 38% vs. 12% p = 0.003
  - More flat 28.6% vs. 4.9% p = 0.0007

<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>Difference (x-fold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiesslich (2003)</td>
<td>University of Mainz, Germany</td>
<td>165</td>
<td>MB</td>
<td>32</td>
<td>10</td>
</tr>
<tr>
<td>Rutter (2004)</td>
<td>St. Mark’s Hospital, Harrow, UK</td>
<td>100</td>
<td>IC</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Hurlstone (2005)</td>
<td>St. James’s University Hospital, Leeds, UK</td>
<td>324</td>
<td>IC</td>
<td>69</td>
<td>24</td>
</tr>
<tr>
<td>Kiesslich (2007)</td>
<td>University of Mainz, Germany</td>
<td>153</td>
<td>MB</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Marion (2008)</td>
<td>Mount Sinai, New York, USA</td>
<td>102</td>
<td>MB</td>
<td>17</td>
<td>9</td>
</tr>
</tbody>
</table>
Recent Meta-Analysis
Chromoendoscopy with targeted biopsy leads to increased efficacy

- 6 Articles contained all data on dysplasia, targeted, flat polyps
- Meta-analysis of 1277 patients of CE
- Leads to 7% (95% CI 3.3 to 10.3%) more dysplasia
- NNT to find another patient with at least one dysplasia 14.3
- Increased the likelihood of detecting any dysplasia 9 x when compared WL
- Detecting non-polypoid dysplasia 5x higher

Challenges to Chromoendoscopy in IBD

- Perception of time consuming and expensive
- Unclear if it changes outcomes (cancer or mortality)
- Many patients don’t “qualify” for it due to poor prep or too much inflammation
- No defined training pathway
**Chromoendoscopy is it to long?**

- Meta-analysis increased procedure time by 11 minutes overall. At experience centers.
- Rutter study tandem overall withdrawal time of 21 minutes.

**Narrowing band Imaging is not Superior to Conventional Colonoscopy for Dysplasia Detection in UC**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Total number of dysplasia</th>
<th>NBI</th>
<th>WLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dekker et al. (2007)</td>
<td>Tandem</td>
<td>42</td>
<td>11</td>
<td>8/11 (73%)</td>
<td>7/11 (64%)</td>
</tr>
<tr>
<td>Van den Broek et al. (2011)</td>
<td>Tandem</td>
<td>48</td>
<td>11</td>
<td>8/11 (73%)</td>
<td>9/11 (82%)</td>
</tr>
<tr>
<td>Ignjatovic et al. (2012)</td>
<td>Parallel group</td>
<td>112</td>
<td>5/56 (9%)</td>
<td>5/56 (9%)</td>
<td></td>
</tr>
</tbody>
</table>

1. Proportion of total dysplastic lesion detected overall
2. Proportion of patient with at least one dysplastic lesion.
High Definition matters.

HD chromo vs. HD white Light

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

<table>
<thead>
<tr>
<th>Patients with Dysplasia</th>
<th>Dysplastic Lesions</th>
<th>Non-polypoid Dysplastic Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD Chemo</td>
<td>21.3% (16/75)</td>
<td>100% (22/22)</td>
</tr>
<tr>
<td>HD WL</td>
<td>9.3% (7/75)</td>
<td>45.5 (10/22)</td>
</tr>
</tbody>
</table>

Picco IBD 2013
SURFACE recommendations for chromoendoscopy

- Strict patient selection
- Avoid active disease
- Risk for CRC
- Unmask the mucosal surface
- Excellent bowel prep; remove mucus and debris
- Reduce peristaltic waves
- Glucagon 1mg in cecum
- Full-staining length of the colon
- Augmented detection with dyes
  - 0.4% indigo carmine; 0.1% methylene blue
- Crypt architecture analysis
  - Pit pattern III/IV of concern
- Endoscopic targeted biopsies
  - Biopsy all mucosal alterations, especially pit pattern III/IV

Adequate preparation
Inflamed Colon Chromo not adequate

Inflamed Colon Chromo not adequate

Inflamed Colon Chromo not adequate

Source: Gastrointestinal Endoscopy Clinics of North America 2014; 24:483-520

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Inflammatory Polyps

Inflammatory Polyps

Inflammatory Polyps

Source: Gastrointestinal Endoscopy Clinics of North America 2014; 24:483-520

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Stricturing disease

Stricturing disease

Stricturing disease

Source: Gastrointestinal Endoscopy Clinics of North America 2014; 24:483-520

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White out

Signs of Non-polypoid colorectal Neoplasms in IBD

- Slightly raised lesion
- Active friability
- Glands toward center

Dyscrasia (villous polyps)
How I can perform chromoendoscopy?

- Follow surface recommendations
- Once reach cecum put methylene blue or indigo in water bottle
- Consider glucagon
- Spraying in segmental fashion every 20-30cm
- Excess dye is suctioned, reinsert colonoscope to proximal segment
- Indigo settle in seconds, methylene blue 60 seconds to be absorbed

How do I perform Chromoendoscopy?

2 Vials of methylene blue in 500ml of water

<table>
<thead>
<tr>
<th>Purpose of IBE</th>
<th>Mixture</th>
<th>Depth of blue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection</td>
<td>2 Ampules with 250ml of water</td>
<td></td>
</tr>
<tr>
<td>Punched Viewing</td>
<td>1 Ampule with 25ml of water</td>
<td></td>
</tr>
<tr>
<td>Submucosal Injection</td>
<td>10 Drops with 100ml of same</td>
<td></td>
</tr>
</tbody>
</table>
I Don’t want all your procedures. You can learn chromoendoscopy?

- Mayo clinic study
- 6 endoscopist no experience of dysplasia surveillance in UC
- Reviewed atlas of neoplastic and non-neoplastic with WLE and CE along with video samples
- Measured withdrawal time from cecum and accuracy of image interpretation (did not include polypectomy)

It’s going to be longer, initially.

- Learning curve
- 31 minutes for fewer than 5 procedures completed.
- 19 minutes for more than 15 procedures completed

Excellent inter-observer agreement among non-expert endoscopic in detection and interpretation of lesions detected by CE

How I can start?

- ASGE Online learning library
- Free video on: Chromoendoscopy with Targeted Biopsy to Detect Nonpolypoid Colorectal Neoplasms
- Atlas of chromoendoscopy
- Detection of Nonpolypoid (Flat and Depressed) Colorectal Neoplasms in Patients With Inflammatory Bowel Disease
- Gastrointestinal Endoscopy Clinics Volume 24, Issue 3
- An Atlas of the Nonpolypoid Colorectal Neoplasms in Inflammatory Bowel Disease
- Review previous pictures along with pathology
How I can start?

- Learning curve
  - Consider transition period of CE with targeted and random biopsy
  - One study showed endoscopist were partnered for first 5 cases procedure time plateaued at 15 cases
- Time allotment
  - Consider initially during learning curve period double colonoscopy time slot.

Stay tuned for new position statement

My approach now to Chromoendoscopy

- WHO:
  - All patients undergoing colonoscopy for colorectal cancer surveillance
- PREP: needs to be clean and in remission
- HOW: Indigo in water bottle
  - 60 minute slot at DHC.
What I do in 2014

- Follow the British Guidelines
  - Patients with highest risk of IBD associated colorectal neoplasia should undergo annual surveillance.
  - Lower risk patients can undergo surveillance at less frequent intervals every 2-5 years.
- Dye base chromoendoscopy with targeted biopsies maximizes colorectal neoplasia detection during surveillance colonoscopy.
- European and Australian guidelines agree that this is the surveillance method of choice.
- Most US guideline endorse with targeted biopsy as an option for surveillance.

How to use surveillance now.

- Use random biopsies as alternative in patients with poor prep and/or multiple pseudopolyps.
- Endoscopically visible lesions that are well circumscribed and amenable to endoscopic resection with no evidence of dysplasia in the surrounding flat mucosa or elsewhere in the colon are appropriate for continued colonoscopic surveillance.

Summary

- The risk of Colorectal cancer is less than previously thought.
- Personalize colorectal cancer surveillance for IBD patients.
  - Based on endoscopic findings and other risk personally surveillance intervals.
  - Random biopsies for surveillance are of limited utility.
- Surveillance colonoscopy in IBD involving colon is still necessary.
  - Use chromoendoscopy due to is superiority in finding dysplasia.
Questions?