Accreditation

• This event has been approved as an accredited (Section 1) group learning activity as defined by the Maintenance of Certification program of the RCPSC. It has been produced under RCPSC guidelines for the development of co-developed educational activities between CAG and Takeda Canada Inc.
Learning Objectives

At the end of this session, participants will be able to:

• Review data on new biologic treatment options, their advantages/disadvantages and treatment algorithm

• Summarize the data on the need for dysplasia surveillance including which patients to surveil and how best to monitor such patients

• Understand the correlation between symptoms and mucosal disease activity, and describe what is meant by mucosal healing

• Describe the markers used to assess mucosal healing, and the patients in whom mucosal healing should be the treatment target
Faculty

Co-Chairs

Brian Bressler, MD, MSc, FRCPC
Director, Advanced IBD Training Program
Clinical Assistant Professor of Medicine, Division of Gastroenterology
University of British Columbia

John Marshall, MD, MSc, FRCPC, AGAF
Professor of Medicine (Division of Gastroenterology)
McMaster University
Chief of Clinical Gastroenterology Service
Hamilton Health Sciences
Faculty

Speakers

**Brian Feagan, MD, FRCPC**
Director, Robarts Clinical Trials
Professor of Medicine, Epidemiology & Biostatistics
University of Western Ontario
London Health Sciences Centre
Robarts Research Institute

**David Rubin, MD, FACG, AGAF, FACP**
Professor of Medicine
Co-Director, Inflammatory Bowel Disease Center
Interim Chief, Section of Gastroenterology, Hepatology and Nutrition
University of Chicago Medicine

**Mark Silverberg, MD, PhD, FRCPC**
Associate Professor of Medicine, University of Toronto
Staff Gastroenterologist, Mount Sinai Hospital IBD Group
Senior Investigator, Lunenfeld-Tanenbaum Research Inst
Zane Cohen Centre for Digestive Diseases
Dysplasia Surveillance: Do we need it?

David Rubin, MD, FACG, AGAF, FACP
Learning objectives:

This presentation will address the following:

1. Why new data suggests that in 2014 we may no longer need to perform dysplasia surveillance in 2014,

2. In which patients with UC we should consider dysplasia surveillance, and

3. How best to survey those patients with UC that require such monitoring.
The IBD-Cancer Prevention Formula

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

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

**Effective Prevention Strategies**
- Pts and MDs implement strategies
- Colectomy
- Polypectomy
- Chemoprevention

**Outcome of interest**
- ↓ Cancer
- ↓ Mortality
- ↓ Colectomy
- ↑ HRQoL
Arguments for and against Colorectal Cancer Surveillance in IBD

Why we should survey
• Cancer does occur in some patients, and they are younger in general than non-IBD CRC
• Risks are well-defined
• A surveillance approach is described and has been refined

Why surveillance may not be needed
• More recent studies suggest overall risk of CRC may not be increased compared to population
• Mortality benefit has not been shown
• Surveillance is expensive and inefficient

Is there a compromise?
Cumulative Risk of Developing CRC in UC
Historical Meta-Analysis

CL=confidence limit.
Patients with UC don’t have an increased risk of Cancer.

Methods:
• A total of 1,515 patients were diagnosed with ulcerative colitis (UC) during 1978 – 2002. Patients were followed until 31 December 2010.
• Age and sex matched cohort.

Results
• Patients with UC were not at increased risk of cancer overall (SIR, 1.12; 95 % CI, 0.97 – 1.28)
• despite increased risk of prostate cancer (SIR, 1.82; 95 % CI, 1.17 – 2.71).

Cumulative Risk of CRC Among 376 UC Patients From Olmsted County, Minnesota, 1940-2001

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

No Overall Cancer or CRC Risk in Danish population-based cohort (22,290 person-years)

Table 5. SMR and 95% CI for Cancer in General According to Age at Diagnosis, Disease Extent at Diagnosis, and Age and Disease Extent in Combination as Observed Among Men and Women With UC Diagnosed in Copenhagen County (1962–1987) and Followed-up Until 1997

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed cancers</td>
<td>Expected cancers</td>
</tr>
<tr>
<td>Total cohort</td>
<td>64</td>
<td>62.47</td>
</tr>
<tr>
<td>Age at diagnosis (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–29</td>
<td>10</td>
<td>5.91</td>
</tr>
<tr>
<td>30–49</td>
<td>13</td>
<td>17.93</td>
</tr>
<tr>
<td>50–69</td>
<td>32</td>
<td>29.94</td>
</tr>
<tr>
<td>70+</td>
<td>9</td>
<td>8.69</td>
</tr>
<tr>
<td>Disease extent at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proctitis</td>
<td>28</td>
<td>28.71</td>
</tr>
<tr>
<td>Substantial</td>
<td>21</td>
<td>21.82</td>
</tr>
<tr>
<td>Pancolitis</td>
<td>13</td>
<td>9.99</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>1.95</td>
</tr>
<tr>
<td>Substantial or pancolitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–29</td>
<td>6</td>
<td>3.34</td>
</tr>
<tr>
<td>30–49</td>
<td>6</td>
<td>10.12</td>
</tr>
<tr>
<td>50+</td>
<td>22</td>
<td>18.34</td>
</tr>
</tbody>
</table>

*Confidence interval excluding 1.00.

Cumulative Risk of Colorectal Cancer in IBD Referral Center v. Population Based Studies

9 recent population-based studies

323,536 person-years

Standardized Incidence Ratio equal for CD, UC and IBD combined

1.7 (95% CI, 1.3-2.1)

Updated Risk Factors for Dysplasia and Colorectal Cancer in Ulcerative Colitis

• Longer duration of disease
• Greater extent of colonic involvement
• Increased inflammatory activity
• Family history of CRC
• Primary sclerosing cholangitis
• Younger age of diagnosis
• Backwash ileitis
• Mass/stricture
• Prior dysplasia
• Pseudopolyps
• Male gender

Current Guidelines for Cancer Prevention in UC and Crohn’s Colitis are Similar (and out of date...)

- Start at 8-10 years (except PSC)
- Intervals vary
- Biopsies at 10 cm intervals (at least 33)
- Chromoendoscopy not recommended as standard of care, but acknowledged as superior to random biopsies.
- HGD → colectomy
- Polypoid lesions completely removed → vigilant follow-up
- Unresectable/carpet lesions → surgery

## No Mortality Benefit with Surveillance in CUC

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcomes of CRC</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surveillance</td>
<td>No Surveillance</td>
</tr>
<tr>
<td>Karlen 1998</td>
<td>2/40 deaths</td>
<td>18/102 deaths</td>
</tr>
<tr>
<td>Choi 1993</td>
<td>15/19 Duke’s A-B</td>
<td>9/22 Duke’s A-B</td>
</tr>
<tr>
<td>Lashner 1990</td>
<td>4/91 deaths</td>
<td>2/95 deaths</td>
</tr>
<tr>
<td>Cochrane Systematic Pooled Analysis 2004</td>
<td>8/110 deaths</td>
<td>13/117 deaths</td>
</tr>
</tbody>
</table>
Low Yield of Random Biopsies in Colitis Surveillance
Most Dysplasia is Visible with White Light

• **Random biopsies**:1
  - N=167 patients, 466 surveillance colonoscopies
  - 24 of 11,772 random biopsies detected neoplasia (0.2% per-biopsy yield)
  - ~1 in 500 random biopsies

• **Visible dysplasia**2,3:
  - Per lesion sensitivity: 61.6%-77.3%
  - Per patient sensitivity: 78.3%-89.3%

---

Performing a cost-effectiveness analysis: surveillance of patients with ulcerative colitis.

Fig. 1. Incremental cost-effectiveness ratios. The horizontal axis displays discounted quality-adjusted life expectancy in years; the vertical axis displays the average lifetime cost per patient (discounted at the rate of 5%). Each circle represents the result for a particular strategy.

Medical decision analysis for the management of unifocal, flat, low-grade dysplasia in ulcerative colitis

TABLE 4. Effect of the rate of progression from LGD to advanced neoplasia on QALYs and costs for immediate colectomy and enhanced surveillance*

<table>
<thead>
<tr>
<th>Cumulative incidence</th>
<th>Reference no.</th>
<th>Immediate colectomy</th>
<th>Enhanced surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>QALY</td>
<td>Cost ($)</td>
</tr>
<tr>
<td>54% at 5 y</td>
<td>10, 24</td>
<td>20.1</td>
<td>75,900</td>
</tr>
<tr>
<td>53% at 5 y</td>
<td>15</td>
<td>20.1</td>
<td>75,900</td>
</tr>
<tr>
<td>33% at 5 y</td>
<td>16</td>
<td>20.1</td>
<td>75,900</td>
</tr>
<tr>
<td>10% at 10 y</td>
<td>17</td>
<td>20.1</td>
<td>75,900</td>
</tr>
<tr>
<td>0% at 18 y</td>
<td>43</td>
<td>20.1</td>
<td>75,900</td>
</tr>
<tr>
<td>0% at 18 y†</td>
<td>n/a</td>
<td>21.6</td>
<td>55,900</td>
</tr>
</tbody>
</table>

n/a, Not applicable.

*With prevalence of synchronous cancer or HGD of 28% at initial diagnosis of LGD.
†Prevalence of synchronous cancer set to zero, and all incidences of progression set to zero for model validation.

Approach to Visible Dysplasia in IBD

The terms “DALM” and “ALM” are being replaced by:
- “polypoid”
- “non-polypoid”
- “flat”
- “invisible” dysplasia

We Should Update our Surveillance Approach

Selective Patients
Better Techniques
What is the utility of enhanced visualization?
Chromoendoscopy is Highly Sensitive and Specific for Dysplasia in UC

- Meta-analysis of 6 randomized controlled trials comparing dye-spray to white light/conventional colonoscopy
- Methylene blue or indigo carmine

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
  - Marion (NYC)
    - Follow-up with colectomy specimens
    - 5 of original 102 had colectomy due to unresectable LGD
      - No CRC

Challenges to Chromoendoscopy in IBD

- Perception of time consuming and expensive (time plus supplies)
- Unclear if it changes outcomes (cancer or mortality)
- Many patients don’t “qualify” for it due to poor prep or too much inflammation
- No consensus on its use in our field
- No defined training pathway or competency requirement
- Comparison to newer high definition scopes not completed
My Approach to Chromoendoscopy

• **WHO:**
  – Pancolonic: High risk (PSC, previous confirmed dysplasia)
  – Segmental: Lesions found and require clarification

• **PREP:** needs to be CLEAN and in remission

• **TYPE:** Methylene blue diluted (my preference)

• **HOW:**

• **FOLLOW-UP:** Depends...
Narrow 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>NBI</th>
<th>WLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dekker et al. (2007)</td>
<td>Tandem</td>
<td>42</td>
<td>8/11(^a) (73%)</td>
<td>7/11(^a) (64%)</td>
</tr>
<tr>
<td>Van den Broek et al. (2011)</td>
<td>Tandem</td>
<td>48</td>
<td>8/11(^a) (73%)</td>
<td>9/11(^a) (82%)</td>
</tr>
<tr>
<td>Ignjatovic et al. (2012)</td>
<td>Parallel group</td>
<td>112</td>
<td>5/56(^b) (9%)</td>
<td>5/56(^b) (9%)</td>
</tr>
</tbody>
</table>

\(^a\)Proportion of total dysplastic lesions detected overall; \(^b\)Proportion of patients with at least one dysplastic lesion.

Risk Stratification of Dysplasia in Colitis

Guide Follow-up and Colectomy Recommendations

Pt/disease-related factors:
- PSC
- Family history of CRC
- Duration
- Degree of inflammation over time and on last exam
- Male v Female

Dysplasia-related factors:
- GRADE:
  - IND vs. LGD vs. HGD
- MORPHOLOGY:
  - Flat vs. Polypoid
  - “Invisible” vs. raised
- FIELD EFFECT/SYNCHRONICITY:
  - Unifocal vs. multifocal
- LONGITUDINAL FOLLOW-UP?
  - Dysplasia on a single exam vs. metachronous lesions on serial exams

STAY TUNED: International Consensus Meeting on Colorectal Neoplasia in IBD, March 2014, San Francisco
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

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

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

FDR, first-degree relative; PSC, primary sclerosing cholangitis
British Society Guidelines 2010

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5 Years

3 Years

1 Year

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OR dysplasia in past 5 years declining surgery
OR PSC / transplant for PSC
OR family history CRC in FDR aged <50

5 Years
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

3 Years

1 Year
Other Considerations
Patient preference, multiple post-inflammatory polyps, age and comorbidity, accuracy and completeness of examination

FDR, first-degree relative; PSC, primary sclerosing cholangitis

Summary: Surveillance for CRC in IBD
Should We or Shouldn’t We?

• The old fashioned information and approach is outdated and needs updating
  – Risks are lower in some patients
  – Random biopsies for surveillance are of limited utility.
  – Cost effectiveness is questionable with current approaches
• Surveillance colonoscopy in UC is still necessary.
  – Define “at risk” patients by multiple risk factors, including inflammation
  – Use enhanced visualization
• The impact of controlled inflammation and improved technology will result in modified approaches going forward