“Advanced Techniques for Dysplasia Detection in Chronic Colitis”

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11/9/12
Outline

• Pathogenesis and Natural History of Dysplasia/CRC
• Epidemiology and Risk Factors for Dysplasia/CRC
• Screening Techniques for Dysplasia/CRC
  – Random biopsy
  – Targeted biopsy
  – Red Flag and advanced techniques
• Guidelines/Recommendations
Indefinite for Dysplasia

- Nuclear changes typical of low grade dysplasia, but with active inflammation

- This lesion is considered ‘indefinite’ because it cannot be reliably distinguished from reactive atypia
Low Grade Dysplasia

- Low grade dysplasia is a cytologic change in the upper crypt and surface epithelium.
- Enlarged, irregular hyperchromatic nuclei are typically confined to the basal half of the involved epithelial cell.
High Grade Dysplasia

- Markedly irregular nuclei occupy basal and apical cytoplasm
- Architectural disorder is typical
Interobserver Agreement for Dysplasia is Low

<table>
<thead>
<tr>
<th>Category</th>
<th>Kappa Digital</th>
<th>Kappa Old</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>0.51</td>
<td>0.46</td>
<td>Good</td>
</tr>
<tr>
<td>Indefinite</td>
<td>0.18</td>
<td>0.27</td>
<td>Poor</td>
</tr>
<tr>
<td>LGD</td>
<td>0.36</td>
<td>0.51</td>
<td>Poor</td>
</tr>
<tr>
<td>HGD</td>
<td>0.54</td>
<td>0.45</td>
<td>Good</td>
</tr>
<tr>
<td>Overall</td>
<td>0.40</td>
<td>0.43</td>
<td>Fair</td>
</tr>
</tbody>
</table>

Diagnosis of dysplasia should be made only after review by 2 pathologists.

Odze RO, et al., *Mod Pathol* 2002
Dysplasia Associated Like Mass (DALM)
Adenoma-Like DALM
Post Inflammatory Polyp or Pseudopolyp
Cumulative Risk of Developing CRC in UC

CL = confidence limit.

Rutter, MD, et al. Gastroenterology 2006
Who’s At Risk?
Risks of Dysplasia or CRC in UC

• Longer duration of disease
• Greater extent of disease
• Family history of CRC\(^1\)
• Primary sclerosing cholangitis\(^2\)
• Increased activity of disease\(^3\)

Probability of Finding Cancer

If Colectomy Done Immediately

- DALM: 43% (17/40)
- HGD: 42% (10/24)
- LGD: 19% (3/16)
- Negative: NA

If Colectomy Done at Follow-up

- DALM: NA
- HGD: 32% (15/47)
- LGD: 8% (17/204)
- Negative: 9% (9/95)

Progression of LGD to HGD or Cancer after LGD

<table>
<thead>
<tr>
<th>Study</th>
<th>Hospital</th>
<th>LGD (n)</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connell (94)</td>
<td>St. Mark’s</td>
<td>9</td>
<td>54% @ 5 yrs</td>
</tr>
<tr>
<td>Ullman (03)</td>
<td>Mount Sinai</td>
<td>46</td>
<td>53% @ 5 yrs</td>
</tr>
<tr>
<td>Ullman (02)</td>
<td>Mayo Clinic</td>
<td>18</td>
<td>33% @ 5 yrs</td>
</tr>
<tr>
<td>Rutter (06)</td>
<td>St. Mark’s</td>
<td>36</td>
<td>25% @ 5 yrs</td>
</tr>
<tr>
<td>Lindberg (96)</td>
<td>Huddinge</td>
<td>37</td>
<td>35% @ 20 yrs</td>
</tr>
<tr>
<td>Lim (03)</td>
<td>Leeds, UK</td>
<td>29</td>
<td>10% @ 10 yrs</td>
</tr>
<tr>
<td>Befrits (02)</td>
<td>Karolinska</td>
<td>60</td>
<td>2% @ ~10 yrs</td>
</tr>
</tbody>
</table>
### Severity of Inflammation is a Risk Factor for CRC in UC

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (N=68)</th>
<th>Cases (N=136)</th>
<th>Odds Ratio of CRC (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate Analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colonoscopy inflammation score(^a)</td>
<td>1.89 (0.52)</td>
<td>2.22 (0.78)</td>
<td>2.54 (1.45-4.44)</td>
<td>0.001</td>
</tr>
<tr>
<td>Histologic inflammation score(^a)</td>
<td>2.05 (0.41)</td>
<td>2.38 (0.56)</td>
<td>5.13 (2.36-11.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Multivariate Analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histologic inflammation score(^a)</td>
<td></td>
<td></td>
<td>4.69 (2.10 – 10.48)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>All other factors</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
</tbody>
</table>

\(^a\)Mean (SD); odds ratio is for a 1-unit increase in score.  
Dysplasia in IBD

- 40 biopsies sample <0.05% of the colon!
- 32 biopsies have a 90% sensitivity to detect dysplasia or cancer if present
- 64 biopsies needed for 95% sensitivity!

Rubin, CE et al. Gastroenterology 1992
What is Done?

- In meta-analysis of 20 surveillance studies – average is 18 biopsies (range 9-24)

Thomas, T., Aliment Pharmacol Ther 2007
Random Biopsy Protocols

• Yield of random biopsies obtained from chromoendoscopy studies
  – No dysplasia detected in nearly 3,000 random biopsies
  – 18 dysplastic lesions detected from 12,482 random biopsies
  • 693 biopsies needed to detect one case of dysplasia
  • One case per 38.5 colonoscopies

Rutter, MD et al. Gut 2004
Hurlstone, DP et al. Endoscopy 2005
Colonoscopy Decreases Mortality from CRC in Patients with Chronic Colitis

5 Year Survival

Connell, WR et al. Gastroenterology 1994
Standard Definition Scopes vs. HD

- SD scope
  - Resolution of 367,000 pixels

- HD scopes
  - Resolution of 850,000 pixels
Is Dysplasia Visible at Colonoscopy?

- Retrospective review of dysplasia identified via targeted vs. non-targeted biopsies
- 525 patients underwent 2204 colonoscopies
- 110 dysplastic areas identified in 56 patients
- 77% were macroscopically visible

Rutter, MD et al. Gastrointest Endosc 2004
Red Flag Techniques-
Chromoendoscopy

• Indigo carmine
  – Provides a surface coating
  – Highlights abnormalities in mucosal contour

• Methylene blue
  – Absorbed by normal colonocytes
  – Leaves abnormal areas relatively unstained
Chromoendoscopy vs. Gold Standard

• Experimental (n=87)
  – Methylene blue 0.1%
    • Targeted biopsies
    • Random biopsies-5 every 10 cm
  – Control (n=87)
    • Targeted
    • Random as above

Kiesslich, R et al. Gastro 2003
<table>
<thead>
<tr>
<th></th>
<th>CE</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration</strong></td>
<td>44+/-12</td>
<td>35+/-9</td>
<td>NS</td>
</tr>
<tr>
<td><strong>(min)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Biopsies</strong></td>
<td>42.2</td>
<td>38.2</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Dysplasia</strong></td>
<td>32</td>
<td>10</td>
<td>.003</td>
</tr>
<tr>
<td><strong>LGD</strong></td>
<td>24</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td><strong>HGD</strong></td>
<td>8</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Kiesslich, R et al. Gastro 2003
Chromoendoscopy vs. Gold Standard

- Method A: Non-targeted
- Method B: White light, targeted
- Method C: Methylene blue (0.1%), targeted
- “Back to back” colonoscopy per segment
- N=115
  - 39% had previously documented dysplasia

Marion, JF et al. Am J Gastroenterol 2008
# Procedure Duration

<table>
<thead>
<tr>
<th>Type</th>
<th>Median Time (min)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dye targeted</td>
<td>15:12</td>
<td>5:09-28:35</td>
</tr>
<tr>
<td>Combined total</td>
<td>35:32</td>
<td>10:36-1:10:44</td>
</tr>
</tbody>
</table>

Marion, JF et al. Am J Gastroenterol 2008
LGD or HGD by Method

Marion, JF et al. Am J Gastroenterol 2008

*p=.15**p<.001***p<.0002
Red Flag Techniques - Chromoendoscopy

- Standard colonoscopy prep
  - Quality of the prep is essential
- Mix 15 ml methylene blue with 135 ml of saline (~1:10 dilution)
- Complete exam to terminal ileum/cecum
- Divide colon into 4 segments
  - Spray each segment with methylene blue using spray catheter and 30 cc syringe
  - One segment at time-spray, reinsert, examine
  - Repeat in remaining segments
Application of Methylene Blue
Application of Methylene Blue
Kudo’s Pit Patterns

CCFA and ACG Surveillance Guidelines

• All patients with left sided or pancolonic UC and extensive colonic CD (at least 1/3 of colon involved) for more than 8-10 years should have a screening colonoscopy

• After negative screening colonoscopy, next colonoscopy should be performed in 1-2 years

• After two negative exams, surveillance is repeated every 1-3 years until 20 years of disease; then every 1-2 years

• Patients with PSC should be screening yearly at time of diagnosis

• Patients with UP or ulcerative proctosigmoiditis are not at increased risk

• Patients with a family history of CRC, ongoing endoscopic or histologic inflammation, foreshortened colon, stricture or multiple post inflammatory polyps may benefit from more frequent surveillance


Itzkowitz SH and Present DH. Inflamm Bowel Dis 2005
Suggested Approach to Dysplasia

Adapted from Rubin DT, Turner JH. Clin Gastroenterol Hepatol 2006. 

Dysplasia

Endoscopic appearance

- Flat
- Polyp

Grade?

- High
- Low

Multifocal?

- Yes
- No

Colectomy

Colectomy vs. aggressive follow-up

Colonoscopy ≤6 months

Colonoscopy 1-3 years

Colonoscopy 12 months

Colonoscopy 3-6 months

Indefinite for dysplasia?

- No
- Yes

Active disease?

- No
- Yes

Treat inflammatory activity

Adapted from Rubin DT, Turner JH. Clin Gastroenterol Hepatol 2006.
Summary

• Patients with left sided or pancolonic UC and significant CD colitis are at increased risk for CRC
  – The risk of CRC seems to be less than previously estimated
• Screening probably decreases CRC
• Improved endoscopes and red flag techniques increase detection of dysplasia
• Chromoendoscopy should be considered to replace standard care which includes targeted and random biopsies
• Further advances in visualization may be limited by need for advanced training and increased time for examinations