Dysplasia in Patients Who Refuse Colectomy
Dysplasia on Our Mind
NYSGE December 16, 2015
Dysplasia in Patients Who Refuse Colectomy

Is Colonic Inflammation a Risk Factor for Dysplasia?

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How do you approach Dysplasia in Patients Who Refuse Colectomy?

The approach to Dysplasia in Patients Who Refuse Colectomy is the same as for patients accept surgical options?

They need more education and time and we need to work with them to understand their reluctance (nutrition misconception, concerns regarding anal intercourse)
Goals of Therapy

- Recognize Cancer risk in UC and Crohn’s disease

- Recommend polypectomy and surveillance for *resectable* dysplastic polyps

- Recommend Colectomy for *unresectable* DALMs (HGD and LGD), flat HGD and LGD (multifocal/recurring/unifocal)

- Caveats for unifocal LGD. Meticulous surveillance and minimal active colitis Confirmed with an expert pathologist
Screening and Surveillance in IBD – Ulcerative Colitis

• What is the risk of cancer?
  – Accounts for 1%-2% of all cases of CRCa
  – Causes one sixth of all deaths in UC patients
  – Cumulative probabilities:
    • 2% at 10 years
    • 8% at 20 years
    • 18% by 30 years
    \[
    \begin{align*}
    &0.5-1.0\% / \text{year after 8 years} \\
    \end{align*}
    \]
  – Overall prevalence in any UC pt = 3.7%

Eaden et al. Risk of CRCA in UC-meta-analysis Gut: 48; 526-535
courtesy of Dr Waye
Colorectal Cancer in Ulcerative and Crohn’s Colitis

Cumulative frequency

Time from onset of IBD (years)

Colitis associated CRC

Risk Factors
• Long Duration
• Anatomic Extent
• PSC
• Severity of inflammation
• Lack of medical follow-up and surveillance
• Family History of CRC

Possible Protection
• 5-ASA
• Folate
• Ursodeoxycholic Acid
• Maintenance Therapy/
  Tight medical control

UC - Distinguishing Features

Colorectal Cancer

- Arises from flat mucosa
- Multiple
- Mucinous
- Infiltrates broadly
- Younger age
- Masked by underlying disease
Molecular Progression of UC to CRC
Is Colitis associated CRC more aggressive?

- Normal Epithelium
- Inflamed Epithelium
- Indefinite Dysplasia
- Low-Grade Dysplasia
- High-Grade Dysplasia
- Cancer

- Aneuploidy
- Sialosyl-Tn
- p53
- K-ras
- C-src
- APC
- Rb and Other TSG
- Microsatellite Instability
Should surveillance strategies for UC and CD patients be the same?
Screening and Surveillance in Crohn’s Disease

- Colorectal Cancer in Crohn’s Disease
- Surveillance examinations in 259 patients
  - Dysplasia in 39 patients (6.6%)
    - 10 = indefinite
    - 23 = low grade
    - 4 = high grade
  - Cancer in 5 patients (2%)
- Pediatric scope helped in Dx of 12-24%

Friedman, Rubin, Bodian, Goldstein, Present, Harpaz Gastro: 2001; 120: 820-826
Screening and Surveillance in IBD – Crohn’s Disease

• CD cancers are more proximal than in UC

• Strictures=10X > risk CRC
  30XUC
  6XCD

Greenstein Mt Sinai J Med 2000;67:227
Goal: Not all strictures are equal.

**Colectomy for strictures?**

- **Ulcerative Colitis:** A fixed stricture is malignant and requires colectomy.

- **Crohn’s Disease:** A fixed stricture may be benign.
  - Peds Colonoscope
  - BE: Smooth stricture continue surveillance
  - Irregular borders requires colectomy
Polyps, Polyps, Polyps

• Do all polyps prompt recommendation for colectomy?

• Can we distinguish polyps that have a high probability for malignancy?
ADENOMATOUS-LIKE POLYP IN ULCERATIVE COLITIS
DALMS IN ULCERATIVE COLITIS
Pseudo-vs.Dysplastic Polyp: Macroscopic differentiation

**PSEUDO**
- Multiple
- Sharp borders
- Smooth surface
- Covered with exudate

**DYSPLASTIC**
- Single or few
- Indistinct borders
- Ceribriform surface
- No exudate
Goal: Individualize the great debates over flat and polypoid dysplasia

What does dysplasia mean for our patient?
LGD means Low(Poor) agreement among pathologists

Kappa Statistic: >75 excellent, >60 good, <60 fair, <40 poor

<table>
<thead>
<tr>
<th>Kappa Statistic</th>
<th>GI Pathologist= 5</th>
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</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.26</td>
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</table>

Evaluation of 74 LGD and 50 Control Slides

Lim et al Gut. 2003; 52: 1127 Leeds, UK
The Threat of LGD in Colitis: While Physicians and Patients Sleep

Figure 1. Cumulative incidence of progression of colorectal neoplasia among 18 patients with UC who were diagnosed with flat LGD. Progression is defined by HGD, raised dysplasia, or cancer. The solid line represents cumulative incidence in the original 18 patients, and the dashed line represents cumulative incidence in the 16 patients confirmed to have LGD after pathology review.

LGD in Ulcerative Colitis.

*Is it really LGD or IND?*

LGD in flat mucosa (60 patients)

repeatedly found in two thirds of our patients often in different colonic segments.

During a mean follow-up of ten years,

No case of progression to HGD in flat mucosa or of cancer

We perform standard surveillance in pts with repeated LGD

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Colectomy for LGD?
Consider the Controversies, Consider Colectomy.

**PRO**

- LGD consider colectomy
  - CRC already present
    Multifocal/Recurrent
    Unifocal?
  - LGD may progress without HGD
  - Cannot differentiate progressors vs nonprogressors

**CON**

- LGD can be monitored
  - LGD is common, progression uncommon
  - Sensitivity/specificity of LGD is low
  - IPAA is not without complications
  - How do pouches really do?
  - Reserve surgery for DALM or HGD

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Colectomy for LGD?
Controversies

Ulcerative Colitis
- TPC/IPAA
- TPC/ileostomy

Crohn’s Disease
- TPC/ileostomy?
- Segmental/resection
- Dare to do IPAA?
HGD in Ulcerative Colitis
High Agreement/No Debate

- HGD requires surgery
  - In flat mucosa
    - Confirmed by another pathologist—YES.
  - In unresectable DALM
    - Confirmed by another Bx—NO, not necessary.

- HGD surveillance
  - Completely excised adenoma
  - NO adjacent dysplasia
Dysplasia in Colitis

- **SURGERY vs. SURVEILLANCE**
  - Decision for colectomy is often an informed discussion between PATIENT and PHYSICIAN
  - DALM (LGD or HGD) = 50% chance of cancer
  - Flat HGD = 42% chance of cancer
  - Flat LGD = 19% chance of cancer
  - Many GI doctors do not opt for surgery unifocal LGD...we now recognize the POTENTIAL malignant risk is NOT to be underestimated. LGD is NOT entirely benign.
Surgery vs Surveillance

Colectomy
- Always recommended for patients with flat HGD, DALMs (LGD and HGD), or cancer
- Sometimes recommended for patients with flat LGD
  - Multifocal—YES
  - Recurrent---YES
  - Unifocal----- ? Confirm LGD not IND
    - Frequent FU and multiple bx

Polypectomy
- Adenoma-like DALM ?

Suggested Management of Dysplasia - 2002

**UC - Dysplastic Lesions**

- **Polyp proximal to area of colitis**
  - Complete polypectomy
  - Continued surveillance

- **Polyp within area of colitis**
  - Completely excised polypectomy
  - No adjacent or remote dysplasia

- **Dysplasia in flat colitic mucosa**
  - Unresectable
  - Adjacent or remote dysplasia

**Continued surveillance** → **Colectomy**
COLONOSCOPY SURVEILLANCE FOR DYSPLASIA

UC - Colorectal Cancer

Surveillance
Surveillance Biopsy Protocol

10 cm

5 cm

Screening and Surveillance in IBD

• What is the surveillance schema?
  – 33 biopsies will find it if present--90% accuracy
  – 56 biopsies will give 95% accuracy
  – Place biopsies of different sites in separate vials
  – Surveillance interval
    • Universal disease, over 8 years, ignore activity & age
    • At 8 yrs, 9 yrs, if no dysplasia, repeat every 2 years
  – Do not biopsy inflammatory polyps
Surveillance Recommendations

• Colonoscopy:
  – After 8-10 years of colitis, annually or biannually with multiple biopsies at regular intervals
  – Evidence is not sufficiently strong to justify different guidelines for left-sided colitis vs pancolitis

Surveillance Recommendations

• Biopsies:
  
  – Four every 10 cms from cecum to rectum
  
  – Additional samples of the rectosigmoid area may be advocated
  
  – Polyps should be assessed and removed separately
    • with sampling of surrounding flat mucosa.

Riddell RH. *Scand J Gastroenterol* Suppl 1990; 175: 177-84.
Confocal Endomicroscopy

• Prospective study of chromoendoscopy with fluorescein dye along with confocal endomicroscopy (n=80) vs standard surveillance colonoscopy (n=73)

• 1° endpoint – detection of dysplasia or intraepithelial neoplasia
  Early detection of dysplasia in 19 cases with smart biopsy vs. 4 cases with standard surveillance

• Conclusion
  Improved accuracy and potentially reduced number of biopsies

Kiesslich R et al. DDW 2005, abstract #483
Surgery

- **Colectomy**
  - Recommended for patients with low-grade dysplasia, high-grade dysplasia, DALMs, or cancer

- **Polypectomy**
  - Completely excisable polyp
  - Adenoma-like DALM ?

Management Prevention Issues

- Control of disease.
- Cancer risk.
- Does tighter control of inflammation decrease cancer risk?
Progression of UC to CRC
Postulated Role of 5-ASA

Normal Epithelium → Inflamed Epithelium → Indefinite Dysplasia → Low-Grade Dysplasia → High-Grade Dysplasia → Cancer

Aneuploidy
Sialosyl-Tn

p53

K-ras
C-src
Microsatellite Instability

5-ASA
NH₂
COOH
OH

APC
Rb and Other TSG
Effect of 5-ASA Use on CRC and Dysplasia Risk in UC: A Meta-Analysis

Inclusion Criteria
- Evaluated clearly defined 5-ASA exposure in UC patients
- Reported CRC or dysplasia outcomes
- Provided RR, OR, or data for calculation

6 studies (3 cohort, 3 case-control) 1031 patients (251 CRC cases, 68 dysplasia cases)

CRC Protection
OR = 0.25
(95% CI, 0.15-0.40)

CRC/Dysplasia Protection
OR = 0.47
(95% CI, 0.24 – 0.92)

Prevention of Colorectal Cancer

- Pharmacologic agents (chemoprevention)

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<thead>
<tr>
<th>Sporadic Colon Cancer</th>
<th>Colitis-associated Colon Cancer</th>
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<tbody>
<tr>
<td>Aspirin</td>
<td>Folic Acid</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Ursodeoxycholic acid</td>
</tr>
<tr>
<td>Calcium / Vitamin D</td>
<td>5-ASA</td>
</tr>
<tr>
<td>Folic Acid</td>
<td></td>
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</table>
Folic Acid and Risk for Neoplasia in UC

- Case-control study
- 98 patients with UC
  - Disease proximal to splenic flexure
- Duration: ≥8 years
- 40% of patients used folate ≥6 months
- Result: Although not statistically significant, folate reduced neoplasia risk in dose-dependent manner

Ursodeoxycholic acid (UDCA)

Relative Risk = 0.26 (95% CI, 0.06 - 0.92; p=0.034)

Summary: Dysplasia on our mind

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Always recommended for patients with flat HGD, DALMs (LGD and HGD), or cancer
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  - Multifocal—YES
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**Polypectomy**
Adenoma-like DALM ?/completely excisable polyp

**Meticulous Surveillance Colonoscopy**

Summary: Dysplasia and IBD

Primary prevention with 5-ASA may be beneficial

Encourage maintenance of remission