Screening for Colorectal Neoplasia in Patients with Inflammatory Bowel Disease

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Questions Relevant for Clinicians Who Manage Patients With IBD at Risk for Colorectal Neoplasia

1. Are patients with IBD at increased risk for colorectal cancer?
2. Are there well-substantiated factors other than dysplasia that increase or decrease the risk of CRC in IBD?
3. What is the natural history of dysplasia?
4. Should colectomy be performed for raised dysplasia?
5. Should colectomy be performed for flat dysplasia?

Questions Relevant for Clinicians Who Manage Patients With IBD at Risk for Colorectal Neoplasia

6. Is there sufficient rationale for performing surveillance colonoscopy in patients with IBD?
7. How should surveillance colonoscopy be performed?
8. What role do the newer imaging techniques play in identifying and managing dysplasia?
9. Should chemopreventive agents be used to lower the risk of developing dysplasia or CRC in IBD?
10. Should molecular markers be applied to help stratify patients into low- and high-risk groups?

Increased Risk of Colorectal Cancer in UC Patients

• Meta-analysis of 116 worldwide studies assessing the risk of CRC in UC patients

• Cumulative risk of developing CRC: 2% at 10 yrs, 8% at 20 yrs and 18% at 30 yrs

Is the Risk This High?

- 600 patients with extensive UC followed for 5932 person-years at St. Marks in London
- 30 CRCs detected (annual risk: 0.5% or 1/200)
- Cumulative probability of CRC was 2.5% at 20 years, 7.6% at 30 years and 10.8% at 40 years
- Linear regression suggested that CRC risk declined over the course of the study

Comprehensive meta-analysis of the risk of CRC in ulcerative colitis and Crohn’s disease

- 48 studies included in the meta-analysis
- Included both population based and referral centers
- Included 131,743 persons-years of follow up
- Overall cumulative risk at 10, 20 and 20+ years is 1%, 3% and 7%
- Rate higher in referral centers and those with extensive disease

Cumulative risk in IBD patients

Are patients with IBD at increased risk for colorectal cancer?

- Patients with ulcerative colitis and Crohn’s disease of the colon have an increased risk of developing colorectal cancer.

Are there well-substantiated factors other than dysplasia that increase or decrease the risk of CRC in IBD?

- Disease duration, more extensive disease, primary sclerosing cholangitis, and a positive family history of sporadic CRC are all associated with an increased risk of CRC.
- Colonic strictures in patients with UC and/or a shortened colon, and/or multiple postinflammatory pseudopolyps increase the risk of CRC.
- Inflammation is a risk factor for progression to colorectal neoplasia.

Limitations of Using Dysplasia as Endpoint

• Interobserver variation
  – Several studies demonstrated only moderate levels of agreement
  – Agreement better for HGD/Negative than LGD/Indefinite
  – Confirm diagnosis by expert GI pathologist

• Scope when IBD quiescent

• Need for patient compliance with colonoscopy

• Dysplasia may be absent in 25-30% of colectomy specimens in patients with cancer
Limitations of Using Dysplasia as Endpoint

• Sampling error
  – Multiple biopsies needed
  – 33 biopsies needed to achieve 90% confidence to detect dysplasia if it is present
  – Many endoscopists take an insufficient number of biopsies
  – At least half of all CRC in UC develop in the rectum or sigmoid colon

• Surveillance offers a *reasonable* chance of detecting dysplasia or early stage cancer
High Grade Dysplasia (HGD)

Review of Ten Prospective Surveillance Trials of 1225 patients

- 42% (10 of 24) of patients with HGD who underwent immediate colectomy had synchronous CRC
- 32% (15 of 47) of patients with HGD who underwent colectomy at a later date had CRC

Bernstein CN, Shanahan F, Weinstein WM. Are we telling patients the truth about surveillance colonoscopy in ulcerative colitis? Lancet 1994;343:71-74
Low Grade Dysplasia

Review of Ten Prospective Surveillance Trials of 1225 patients

• 19% (3 of 19) patients with LGD who underwent immediate colectomy had synchronous CRC

• 8% (17/204) of patients with LGD who underwent colectomy at a later date had CRC

Bernstein CN, Shanahan F, Weinstein WM. Are we telling patients the truth about surveillance colonoscopy in ulcerative colitis? Lancet 1994;343:71-74
Dysplasia: St. Mark’s Experience

- Six hundred patients underwent 2627 colonoscopies (5932 patient-years of follow-up)
- Patients with HGD had a high rate of CRC (36.8%)
- Patients with LGD had a high likelihood of concurrent adenocarcinoma or progression to higher grades of neoplasia
  - 20% (2 of 10) had concurrent CRC at the time of LGD-directed colectomy
  - 19.4% (7 of 36) developed CRC during surveillance
  - In total, 19.6% (9 of 46) of patients with LGD developed CRC, and 39.1% (18 of 46) of patients with LGD developed either HGD or CRC (25)

Should colectomy be performed for flat dysplasia?

• Grade A: There is high certainty that colectomy for flat HGD treats undiagnosed synchronous cancer and prevents metachronous cancer.

• Grade Insufficient: The current evidence is insufficient to assess the balance of benefits and harms of colectomy for flat LGD.

IBD Patient with Flat Dysplasia

Low grade
- Unifocal: Colectomy or Increase Surveillance
- Multifocal: Colectomy

High grade: Colectomy
Dysplasia in IBD

Gross Subtypes

Flat
Endoscopically Invisible

Elevated (DALM)
DALMs (Polypoid or Raised Dysplasia)

Adenoma-like
Endoscopically resectable

Non-adenoma-like
Non endoscopically resectable
### Long term Followup of Polypoid Dysplasia Resected Endoscopically

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>No further polyps</td>
<td>38%</td>
<td>52%</td>
</tr>
<tr>
<td>Additional polyps</td>
<td>58%</td>
<td>48%</td>
</tr>
<tr>
<td>Dysplasia in flat mucosa</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>CRC</td>
<td>4%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Should colectomy be performed for raised dysplasia?

Grade A: High certainty that the magnitude of net benefits is substantial.

- Patients with IBD and a non–adenoma-like dysplasia associated lesion or mass should be treated with colectomy.
- Patients with IBD and an adenoma-like dysplasia-associated lesion or mass, and no evidence of flat dysplasia elsewhere in the colon, can be managed safely by polypectomy and continued surveillance.

DALMs (Polypoid or Raised Dysplasia)

- Adenoma-like
  - Outside colitis: Polypectomy, Regular surveillance
  - Inside colitis
- Non-Adenoma-like (broad-base, irregular)
  - Inside colitis
  - Colectomy
  - Polypectomy, Absence of flat dysplasia, ? Increase surveillance
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.

How should surveillance colonoscopy be performed?

- The technique of surveillance colonoscopy in patients with IBD should include extensive biopsies of all anatomic segments of colorectal mucosa.
- Although there are inadequate data available to recommend optimal surveillance intervals, intervals of 1 to 3 years are suggested.
- Careful inspection of the mucosa along with a sufficient number of biopsy specimens should be obtained from all anatomic segments of the colon.

Is Most Dysplasia in Ulcerative Colitis Visible at Colonoscopy?

- Retrospective study of 525 UC patients from 1988 through 2002 (2204 surveillance colonoscopies) which assessed the proportion of dysplasia that was detected macroscopically.
- 110 neoplastic areas were detected in 56 patients.
- 85 (77.3%) were macroscopically visible at colonoscopy, and 25 (22.7%) were macroscopically invisible.
- Fifty patients (89.3%) had macroscopically detectable neoplasia, and 6 (10.7%) had macroscopically invisible lesions.

Chromoendoscopy

- Improves the detection of subtle colonic lesions, raising the sensitivity of the endoscopic examination.
- Chromoendoscopy with or without a magnifying colonoscope can improve lesion characterization, increasing the specificity of the examination.
- Crypt architecture can be categorized using the pit pattern, aiding differentiation between neoplastic and non-neoplastic changes, and enabling the performance of targeted biopsies.
- Provides a more accurate diagnosis of the extent of disease and inflammatory activity.

## Controlled Studies on the Use of Chromoendoscopy in Patients with Ulcerative Colitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Dye</th>
<th>Number of lesions</th>
<th>Difference (x-fold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kiesslich et al. (2003)</td>
<td>165</td>
<td>MB</td>
<td>42 (32 vs 10)</td>
<td>3.07</td>
</tr>
<tr>
<td>Hurlstone et al. (2004)</td>
<td>324</td>
<td>IC and magnification</td>
<td>93 (69 vs 24)</td>
<td>3.81</td>
</tr>
<tr>
<td>Rutter et al. (2004)</td>
<td>100</td>
<td>IC</td>
<td>7 (7 vs 0)</td>
<td>4.50</td>
</tr>
<tr>
<td>Kiesslich et al. (2007)</td>
<td>153</td>
<td>MB and Confocal Endomicroscopy</td>
<td>23 (19 vs 4)</td>
<td>4.75</td>
</tr>
<tr>
<td>Marion et al. (2008)</td>
<td>102</td>
<td>MB</td>
<td>20 (17 vs 9)</td>
<td>5.66</td>
</tr>
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</table>

What role do the newer imaging techniques play in identifying and managing dysplasia?

- The sensitivity of chromoendoscopy for detecting dysplasia is higher than white light endoscopy in the hands of endoscopists who have expertise with this technique.
- The natural history of chromoendoscopically detected dysplasia is unknown.
- Additional studies are needed to evaluate the efficiency of other imaging methods, such as narrow band imaging and confocal endomicroscopy, in detecting dysplasia.

Should chemopreventive agents be used to lower the risk of developing dysplasia or CRC in IBD?

Grade A: High certainty that the magnitude of net benefits is substantial.

- Ursodeoxycholic acid has demonstrated a significant reduction in CRC in patients with UC who also have PSC*.

Grade B: Moderate certainty that the magnitude of net benefits is moderate.

- Aminosalicylates are chemopreventive against CRC.

* Recently published data suggests high dose ursodeoxycholic acid may increase risk of CRC in PSC patients

Should chemopreventive agents be used to lower the risk of developing dysplasia or CRC in IBD?

Grade D: High certainty that the magnitude of net benefits is negative.

– Oral or topical corticosteroids, while demonstrating antineoplastic effects in 2 studies, are associated with too many side effects to warrant use as chemopreventive agents.

Grade Insufficient: No recommendation, insufficient evidence to recommend for or against the use of thiopurines, supplements, or statins.

– Azathioprine or 6-mercaptopurine has not been consistently associated with lower rates of CRC.
– Folic acid supplements, calcium, multivitamins, or statins have not been consistently associated with lower rates of CRC.

Should Molecular Markers Be Applied to Help Stratify Patients Into Low-Risk and High-Risk Groups?

Grade Insufficient: No recommendation; insufficient evidence to recommend for or against the use of molecular markers.

- Molecular markers should not be applied to help stratify patients into low-risk and high-risk groups at this time.

Surveillance Colonoscopy

- All patients should undergo a screening colonoscopy a maximum of 8 years after onset of symptoms
  - Regardless of extent of disease at diagnosis
  - Multiple biopsies to assess microscopic extent of inflammation

- Ulcerative proctitis or proctosigmoiditis are not considered at increased risk for IBD-related CRC
  - Manage on the basis of average-risk recommendations

- Patients with extensive or left-sided colitis should begin surveillance within 1 to 2 years after the initial screening colonoscopy

Surveillance Colonoscopy

- The optimal surveillance interval has not been clearly defined
  - After 2 negative examinations survey every 1 to 3 years

- Representative biopsy specimens from each anatomic section of the colon should be obtained
  - Minimum of 33 biopsy specimens be taken in pancolitis patients

- Chromoendoscopy with targeted biopsies is recommended as an alternative to random biopsies for endoscopists who have expertise with this technique
  - Increased sensitivity for detecting dysplasia

Surveillance Colonoscopy

- **Patient with PSC**
  - Survey at time of diagnosis and then yearly
- **Ideally, surveillance colonoscopy should be performed when the colonic disease is in remission**
- **More frequent surveillance examinations:**
  - History of CRC in first-degree relatives
  - Ongoing active endoscopic or histologic inflammation
  - Anatomic abnormalities such as a foreshortened colon, stricture
  - Multiple inflammatory pseudopolyps
- **Same recommendations for patients with Crohn’s colitis who have disease involving at least one third of the length of the colon**

BSG Executive Summary

- All patients with ulcerative colitis or Crohn’s colitis should have a screening colonoscopy approximately 10 years after the onset of colitic symptoms to assess disease extent and other endoscopic risk factors.

- Surveillance colonoscopies should be performed, where possible, when the disease is in remission.
  - Surveillance procedure should not be unduly delayed if remission cannot be achieved.

BSG Executive Summary

- Cancer risk factors
  - Duration and extent of disease, primary sclerosing cholangitis, family history of CRC and endoscopic and histological appearances at colonoscopy

- Screening intervals recommended account for such variables

- Surveillance colonoscopies should be conducted yearly, 3-yearly or 5-yearly accordingly

BSG Executive Summary

- Pancolonic dye spraying with targeted biopsy of abnormal areas is recommended

- If chromoendoscopy is not used, take 2-4 random biopsy specimens every 10cms from the entire colon

- If a dysplastic polyp is detected within an area of inflammation and can be removed in its entirety, it is not necessary to recommend colectomy