Colorectal Cancer in IBD: What is the Latest on Screening, Surveillance, & Treatment?

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Colorectal Cancer Risk in Ulcerative Colitis Patients

- Cancer risk - 5.5%-13.5% cumulative incidence in population-based studies
- Young age makes the relative risk >3 times the general population.
- Confirmatory studies from Sweden (SIR 4.1), Denmark (SIR 3.10), Greece, Germany, & Japan (SIR 9.93)

Karlen P, et al. Am J Gastroenterology 1999;94:1047-52.

Who is at risk?

- Ulcerative colitis and Crohn's colitis
- Extensive disease (proximal to splenic flexure or 30% of colon)
- Long duration of disease (≥7 years)
- Young age at symptom onset
- Primary sclerosing cholangitis
- Chronic inflammation

Pts with risk factors should have more frequent colonoscopy

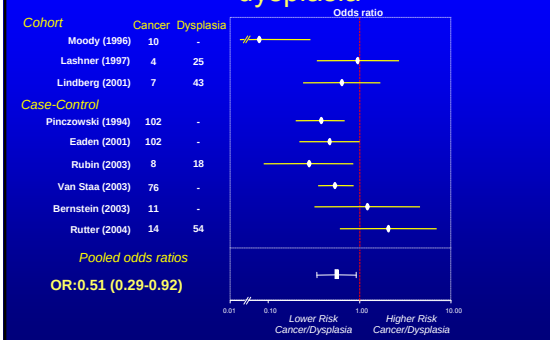
Prevention of Colorectal Cancer

- Primary prevention
  - 5-ASA
  - Folic acid
  - Ursodeoxycholic acid
- Secondary prevention
  - Chromoendoscopy
  - Narrow band imaging
  - Autoflourescence

5-Aminosalicylic Acid

- Decreases arachadonic acid metabolism (both COX & lipoxygenase pathways)
- Inactivates reactive oxygen species
- Increases apoptosis (NF-*k*B suppression)
- Decreases IL-2 production (IL-2 stimulates clonal proliferation of T-cells)
- Activates peroxisome proliferator-activator receptor (PPAR) γ - anti-inflammatory & anti-proliferative

5-ASA use and colorectal cancer or dysplasia



Velayos FS, et al. Am J Gastroenterol. 2005;100:1345-53.

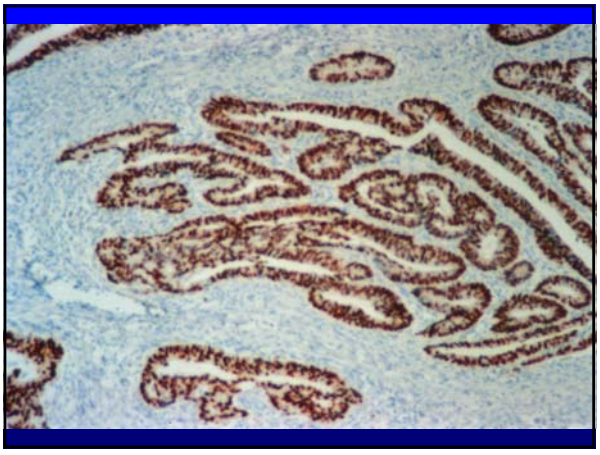
Folic Acid

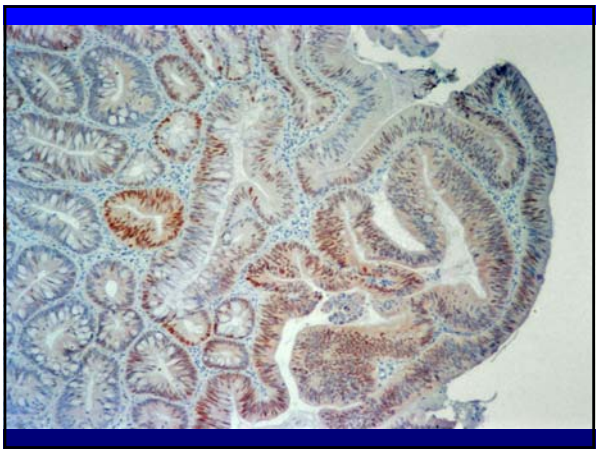
- Folate is essential for regeneration of methionine - purine & pyrimidine synthesis.
- Folate deficiency is associated with DNA hypomethylation, aberrant DNA synthesis & repair, & decreased apoptosis.
- Folate-sensitive fragile sites on genes important for carcinogenesis like p53 suppressor gene
- UC - Folate deficiency from intestinal losses, poor intake, & competitive inhibition of absorption from sulfasalazine

Folic Acid in Ulcerative Colitis

- 1. 99-pt case-control study - folate OR 0.38 (0.12-1.20)
- 2. 67-pt case-control study - OR for 10ng/ml increase in RBC folate - 0.82 (0.68-0.99)
- 3. 98-pt cohort study - RR folate 0.72 (0.28-1.83)
  - Dose-response - RR 0.4mg 0.76, 1.0mg 0.54
  - Dysplasia - RR LGD 0.75, HGD 0.52; cancer 0.45

1. Lashner BA, et al. Effect of folate supplementation on the incidence of dysplasia & cancer in UC. Gastroenterology 1989;97:255-9.
2. Lashner BA. RBC folate is assoc. with the development of dysplasia & cancer in UC. J Cancer Res Clin Oncol 1993;119:549-54.
3. Lashner BA, et al. The effect of folic acid on the risk for cancer or dysplasia in UC. Gastroenterology 1997;112:29-32.

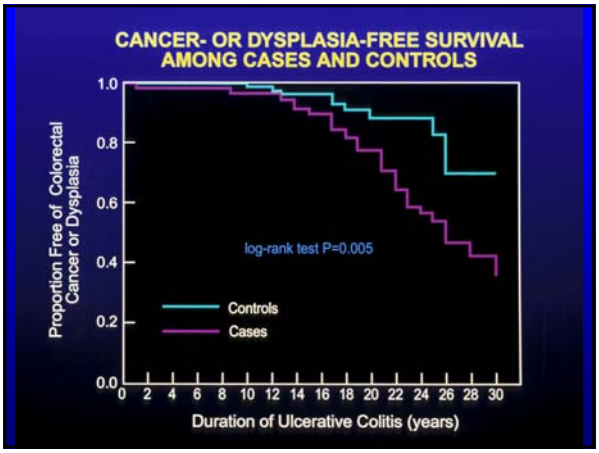




Ursodeoxycholic Acid

- Secondary bile acids are carcinogenic & increased in patients with cholestatic liver disease.
- If the excess cancers are right-sided where 2^0 bile acid concentrations are highest, then either UDCA or OLT could be chemopreventive for CRC.
- Cohort study of 132 PSC pts with UC v. 196 UC pts
- CRC/dysplasia - 33 (25%) cases v. 11 (6%) controls (P<0.001)
- Adjusted RR CRC/dysplasia - 3.15 (1.37-7.27)
- All of excess cancers were proximal to splenic flexure

Shetty K, et al. The risk of cancer or dysplasia in UC patients with PSC. Am J Gastroenterol 1999;94:1643-9.



UDCA for Chemoprevention of CRC

- 1. 59-pt cohort study - 41 (69%) on UDCA
  - Dysplasia in 32% of UDCA users v. 72%
  - Adjusted OR UDCA 0.14 (0.03-0.64)
- 2. 52-pt RCT of UDCA for PSC
  - Dysplasia in 10% of UDCA v. 35% placebo
  - RR CRC/dysplasia - 0.26 (0.06-0.92)
- 3. 120-pt cohort study – 28 (23%) on UDCA
  - Dysplasia or cancer in 29% of UDCA users v. 27%
  - Adjusted RR UDCA 0.59 (0.26-1.36)

1. Tung BY, et al. Ann Intern Med 2001;134:89-95.
2. Pardi DS, et al. Gastroenterology 2003;124:889-93.
3. Wolf JM, et al. Aliment Pharmacol Ther 2005;22:783-8.

IBD-Related CRC Chemoprevention Recommendations

5-ASA 2g
Folic acid 0.4-1.0mg
UDCA 1200mg (PSC)

Cost-Effective Surveillance Colonoscopy

- Markov model simulating a cohort of 35 yo men with ulc colitis, lifetime CRC 30% without surveillance or 5-ASA
- Without 5-ASA – Annual surveillance is ideal strategy $69,100/QALY
- With 5-ASA – (49% reduction in CRC)
  - Surveillance every 3 yrs - $63,400/QALY
  - Surveillance every 2 yrs - $147,500/QALY
  - Surveillance every year - $974,000/QALY

Rubenstein JH, et al. Am J Gastroenterol 2009;104:2222-32.

Newer Endoscopic Techniques to Better Detect Dysplasia

- Current practice – ≥ 32 random & targeted biopsies throughout colon
  - Chromoendoscopy
  - Narrow Band Imaging
  - Autofluorescence
  - Confocal endomicroscopy

Chromoendoscopy

- Absorptive stains
  - Methylene blue (with a mucolytic)
  - Lugol's solution
- Reactive stains
  - Congo red
  - Phenol red
- Contrast stains
  - Indigo carmine

Chromoendoscopy

- RCT - 165 patients with UC > 8 years - conventional surveillance v. chromoendoscopy
- 0.1% methylene blue staining prior to biopsy - taken up by epithelial cells, stable staining pattern, pit pattern visible in polypoid lesions
- Dysplasia - 38% v. 12% (P=0.003)

Kiesslich R, et al. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia & CRC in UC. Gastroenterology 2003;124:880-8.

Findings

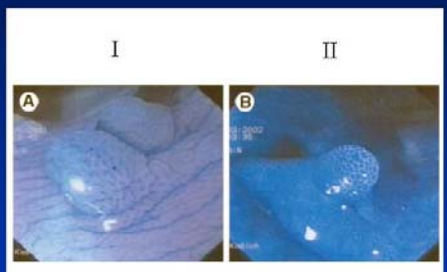
Table 5. Intraepithelial Neoplasias and Cancers

	Group A	Group B	P[a]
n	84	81	—
Patients with INs	13	6	NS
Total no. of INs[a]	32	10	0.00315
Low-grade INs	24	8	—
High-grade INs	8	2	—
Invasive cancers	3	1	NS
Polypoid INs	8	6	NS
INs in "flat mucosa"[a]	24	4	0.0007

IN, intraepithelial neoplasia.
[a]Fisher exact test.

Group A - Chromoendoscopy

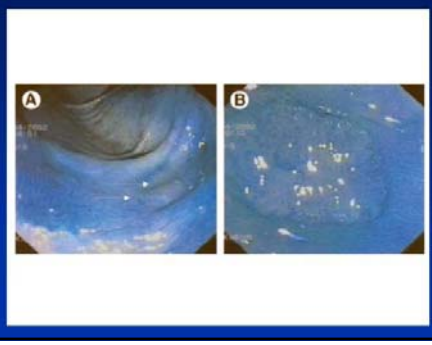
Pit Patterns I & II



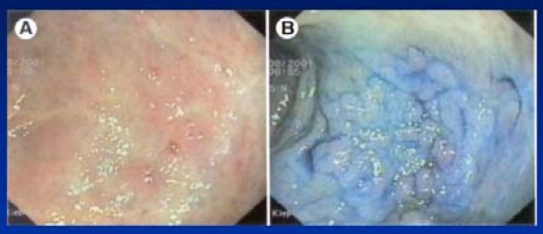
Same as surrounding epithelium

Stellate appearance

Low-grade Dysplasia

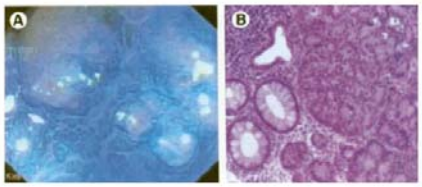


High-grade Dysplasia



Kiesslich R, et al. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia & CRC in UC. Gastroenterology 2003;124:880-8.

Superficial Spreading Cancer



Chromoendoscopy for Mass Lesions

	Dysplasia	No Dysplasia
Pit pattern III & IV	30	6
Pit pattern I & II	2	80

Sensitivity 94%, Specificity 93%

Targeted v. Non-Targeted Bxs

- Tandem colonoscopies, 100 UC pts, routine bxs then indigo carmine-directed biopsies
- Non-targeted bxs – 0/2904 with dysplasia
- Targeted biopsies – 157 in the population
  - No chromo – 2/20 pts with dysplasia
  - Chromoendoscopy
    - 5/55 additional pts with dysplasia
    - 7/114 additional lesions had dysplasia

Rutter MD, et al. Gut 2004;53:256-60.

Cleveland Clinic Experience

	UC	Crohn's Colitis	Indeterminate Colitis
N	27	9	3
Mean age (range)	50 yrs (23-80)	50 yrs (33-65)	56 yrs (33-65)
Mean age with dysplasia (range)	46 yrs (25-66)	57 yrs (51-65)	-
Mean disease duration (range)	18 yrs (6-42)	17 yrs (9-29)	19 yrs (13-23)
Extensive Disease (%)	26 (96%)	-	3 (100%)
PSC (%)	2 (7%)	0	1 (33%)
Mean white light withdrawal time (range)	9 min (6-19)	-	6 min (6)
Mean chromo withdrawal time (range)	40 min (22-50)	-	43 min (36-50)

Kandiel, A.. *Visible Human Journal of Endoscopy* 2008; 7(1):1-7
www.vhjoe.org/Volume7Issue1/7-1-7.htm

All Detected Lesions

- 54 visible lesions with conventional white light colonoscopy
  - 7 (13%) low-grade dysplasia
- 28 additional lesions with chromoendoscopy
  - 2 (7%) low grade dysplasia
- Random biopsies of normal appearing mucosa
  - 1/39 patients had flat low-grade dysplasia with no visible lesions
- No high-grade dysplasia or cancer

Mount Sinai Experience

- 102 patients with WLE (random biopsies) & methylene blue with targeted biopsies
- 17 pts with dysplasia (16 LGD, 1 HGD)
  - WLE – 9 pts detected with targeted bx
  - WLE – 3 pts detected with random bx
  - Chromo – 5 pts detected with targeted bx

Marion JF, Am J Gastroenterol 2008;103:2342-9.

Narrow Band Imaging

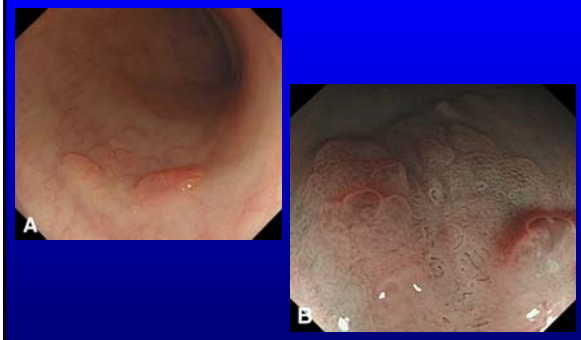
- NBI employs a series of filters to project mostly blue light with shallow penetration into tissues.
- Vascular structures, like polyps and dysplasia, are darkly colored.
- Surrounding mucosa and residual stool are lightly colored.
- Convenient

NBI

- 46 patients with ulcerative colitis, 5 dysplastic lesions were found in 276 areas of flat mucosa that were examined.
- "Tortuous" pattern - 4 cases of dysplasia
- "Villous" pattern – 1 case of dysplasia
- "Honeycomb-like" pattern – no dysplasia

Matsumoto T, et al. Gastrointest Endosc 2007;66:957-65.

Tortuous Pattern - LGD

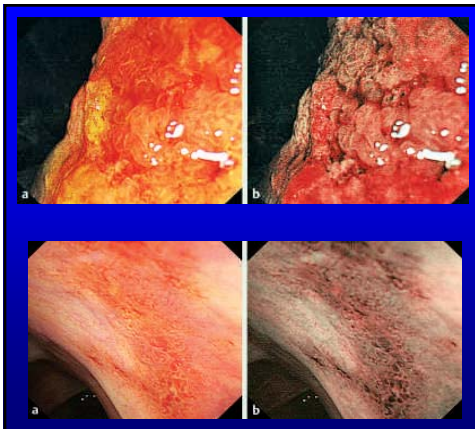


Tortuous Pattern - HGD

NBI

- 42 ulc. colitis pts had surveillance colonoscopy with either NBI or WLE separated by 3 wks.
- 11 patients with dysplasia were identified.
  - 4 pts - both WLE and NBI
  - 4 pts - NBI only
  - 3 pts - WLE only

Dekker E, et al. *Endoscopy* 2007;39:216-21.



Autofluorescence

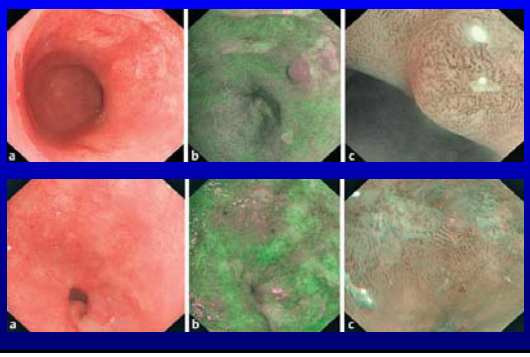
- Fluorophores – mitochondria, lysosomes, submucosal collagen – Red AF
- Chromophores – Hemoglobin – Purple AF
- Non-neoplastic mucosa – Green AF

Barrett's Esophagus

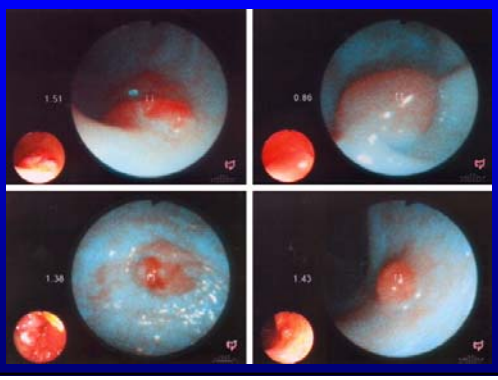
- 20 pts with Barrett's esophagus at high risk for dysplasia
- Autofluorescence - 28 dysplastic lesions
- NBI – 25 (89%) of those lesions detected
- WLE – 17 (61%) of those lesions detected
- Autofluorescence could be even more sensitive in detecting dysplastic lesions than NBI.

Kara MA, et al. *Endoscopy* 2006;38:627-31.
Kara MA, et al. *Gastrointest Endosc* 2006;64:176-85.

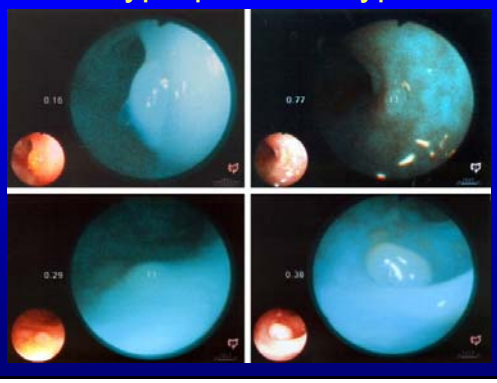
HGD in Barrett's Esophagus



Adenomatous Polyps



Hyperplastic Polyps



Conclusions

- 5-ASA & folic acid should be given for possible chemoprevention, & UDCA in PSC pts.
- Surveillance colonoscopy every 2-3 years
- Random biopsies of normal appearing mucosa are still of benefit for dysplasia surveillance.
- Chromoendoscopy increases the sensitivity of detecting dysplasia in ulcerative colitis pts by less than 2-fold.
- Chromoendoscopy is widely available, inexpensive, & may soon be incorporated into practice.
- NBI & AF are promising, but have not been sufficiently studied.