Dysplasia and colitis

Robert Enns MD FRCPC, Brian Bressler MD

The issue of dysplasia within the setting of chronic colitis is rapidly evolving, and more aggressive endoscopic management and surveillance is clearly being suggested in selected cases (1-3). With the advent of more effective therapies such as tumour necrosis factor inhibitors, it has been suggested that some patients are likely to be managed with medical therapy for longer time periods (before colectomy), possibly resulting in an increased lifetime risk of dysplasia due to the retained colon. Although supportive data for this hypothesis are lacking, there are several new studies that have improved our knowledge in these areas and may lead to increased endoscopic management of certain colonic lesions in this setting.

The cumulative risk of colon cancer in patients with colitis has been an epidemiological debate for many years (4-6). In ulcerative colitis (UC), Eaden et al (7,8) demonstrated a risk of almost 20% at 25 years, giving support to the possibility of early prophylactic colectomy. Others have argued that in an era of more effective medical therapy and more intense patient monitoring, this number may be decreased because inflammation is one of the key risk factors for dysplasia, and by treating the colitis more aggressively, dysplasia risks may be decreased although duration of disease is increased.

RISK-STRATIFYING PATIENTS WITH INFLAMMATORY BOWEL DISEASE

There are many other risk factors to consider in the setting of UC as opposed simply to duration of disease and inflammation. Patients with a family history of disease have at least a twofold increased risk of cancer. Young age of onset (independent of duration of disease) has also been demonstrated to increase the risk. Finally, the extent of disease (ie, risk similar to general population if less than 35 cm of the colon from the anal verge is involved) is critical in determining the risk stratification of patients (8,9). Perhaps the biggest risk of colon cancer in patients with inflammatory bowel disease is related to codiagnosis of primary sclerosing cholangitis (PSC) (10-13). At 25 years, these patients may have a 50% risk of developing colonic cancer and, therefore, early, aggressive surveillance protocols have been recommended.

For colitis in the setting of Crohn's disease (CD), the data are much more recent. One of the problems with all studies in colitis and colorectal cancer risk relates to the documentation of affected bowel. For both UC and CD, the extent of affected colon is considered a risk factor; however, often a clear history of pancolitis or even documentation of the extent of disease is

Dr Brian Bressler is a gastroenterologist and clinical instructor at St Paul's Hospital and the University of British Columbia, Vancouver, British Columbia

only inferred but not endoscopically documented. This makes it difficult, at times, to risk-stratify the patients appropriately. In CD patients who have at least one-third of the colon affected, a recent study (14) demonstrated a 25% risk of developing dysplasia over a 10-year period. This study involved 259 patients and documented seven cancers and six patients with high-grade dysplasia (HGD). A meta-analysis (15) has reviewed all appropriate studies published before 2006 and determined that there is no increased risk of colon cancer in patients with isolated ileal disease; however, individuals with significant colonic disease and 'all comers' with CD had an increased risk (RR 2.5 and 4.5, respectively).

RECOMMENDATIONS AND BIOPSY PROTOCOLS

With the risk factors noted above, both the Crohn's and Colitis Foundation of America and the British Society of Gastroenterology (BSG) have suggested guidelines for screening (7,16). Both suggest beginning surveillance at eight years of disease in affected patients, with more intensive and earlier surveillance in individuals with concomitant PSC. The BSG has recommended a 'staged' surveillance pattern depending on how long the patient has been affected by disease. The frequency of surveillance in their recommendations is every third year during the second decade of disease, every second year during the third decade of disease and every year during the fourth decade of disease. Additionally, the BSG has suggested that initiation of surveillance in patients with isolated left-sided disease is not necessary until the individual has been affected for at least 15 to 20 years.

Although several chemotherapeutic agents (17) (eg, folic acid [18-20]), ursodeoxycholic acid [21,22], nonsteroidal anti-inflammatory drugs and 5-aminosalicylic acid compounds [23-25]) have demonstrated benefit in decreasing risk from dysplasia, most investigators rely heavily on endoscopic biopsy protocols for their reassurance. Typically, four-quadrant biopsies, labelled geographically every 10 cm throughout the colon (minimum of 32 biopsies), is recommended. Because the rectum may be the area at highest risk, more aggressive biopsies of this area are often suggested.

Despite the fact that dysplasia protocols seem to be supported verbally by most endoscopists, the actual practice of the rigorous recommendations is uncommonly followed (26-28). The reasons for this are unclear but increased endoscopic duration may play a critical role. In a similar manner to polyp detection rate and colonoscopy withdrawal in the general screening population, it

St Paul's Hospital, University of British Columbia, Vancouver, British Columbia

Correspondence: Dr Robert Enns, St Paul's Hospital, University of British Columbia, 770-1190 Hornby Street, Vancouver,

British Columbia V6Z 2K5. Telephone 604-688-6332, fax 604-689-2004, e-mail renns@interchange.ubc.ca

Received and accepted for publication April 17, 2009

has been demonstrated that detection rates of flat dysplasias increase with longer procedure times.

WHAT TO DO WITH DYSPLASIA?

There are many terms that have become popular regarding this issue that often confuse the endoscopist. Most importantly, it is critical that the endoscopist describe the areas of affected inflammation and then describe the lesion. Polypoid lesions have been termed disease-associated lesion or mass (DALM) if they reside within an area of affected bowel and are believed to be caused by the inflammation (ie, dysplasia). An adenomatous-like lesion is a polyp (adenomatous) that occurs within the area of affected colon but is believed to be a sporadic lesion. The endoscopic appearance of the lesion is how one distinguishes between these two types of polyps – meaning that the expertise of the endoscopist is of the utmost importance in the making this clinical diagnosis. A sporadic adenoma is a term used to describe a polyp outside the area of inflammation that was not caused by the underlying colitis and has the appearance of a typical polyp.

The difference in these terms is critical because many will argue that DALM is a term that typically has denoted a field defect – often associated with many other areas of dysplasia – in which case a colectomy is mandated. The other lesions described may be sporadic and their removal may simply consist of endoscopic polypectomy.

If one finds a flat, high-grade dysplastic lesion in the colon (usually on random biopsy), the recommendation would be colectomy. If a typical-appearing polypoid lesion is seen and is a discreet polyp without other evidence of dysplasia (biopsies suggested around the polypoid site), and it is completely removed, repeat colonoscopy in three to six months to search for other evidence of dysplasia (which, if present, colectomy would be recommended) could be considered.

If the lesion is flat with low-grade dysplasia, one can either suggest colectomy (especially if multifocal) or repeat the colonoscopy in three to six months to look for other evidence of dysplasia (which, if present, colectomy would be recommended).

If biopsies are indeterminate, repeat endoscopic examinations with appropriate biopsy protocol is recommended (six months later if probably positive indeterminate and one year if probably negative indeterminate). For no dysplasia, repeat colonoscopy with biopsy protocol in one to two years is recommended.

Although these recommendations are widely used, it must be recognized that many other issues can arise that may help guide the physician. The presence of multiple pseudopolyps may limit the ability to survey the colon accurately. The presence of a new luminal stricture in a colon with longstanding colitis is a recommendation for a colectomy in almost all circumstances. Additionally, if the patient has more difficult inflammation to manage, they may be more receptive to colectomy. Finally, some patients tend to become somewhat obsessed with the possibility of developing colon cancer; consequently, their quality of life (with the colon in situ) is dramatically reduced due to their overall concern for an adverse outcome.

MORE CONSERVATIVE MANAGEMENT?

The original study by Blackstone et al (29) in 1981 that followed 112 patients with UC, of which 12 developed DALM lesions, eventually reported that seven of these patients had developed colon cancer. This study was convincing regarding the inherent risk of leaving these colons in situ in this particular group of patients. However, this was a high-risk group of

patients in whom typical tubular adenomas less than 1 cm in size were not considered DALMs.

Subsequently, a more generous approach with dysplasia seemed to be advocated and, therefore, other investigators have not found this high rate of cancer (30). Several studies have suggested a more conservative approach in the setting of typical-appearing adenomas found in colitis (31). In 1999, Rubin et al (32) followed 48 patients with chronic colitis who had adenomas removed (none were flat, none had dysplasia elsewhere in the colon) and found that over a four-year time period none had developed colon cancer but 48% had recurrent polyps. In 2004, Odze et al (33) described 34 patients with UC who had adenomas endoscopically removed and followed for almost seven years. Twenty patients developed recurrent adenomas, one had flat adenoma and one patient with PSC developed colon cancer. More recently, Blonski et al (1) followed 30 patients without flat adenomas (nine of them HGD). Three patients underwent colectomy and six were followed conservatively for longer than six years; there were no cancers that developed.

Ideally, differentiation of higher risk lesions would be easy to perform. Chromosomal changes and microsatellite instability (34-39) are/have been assessed with some promising findings; however, more research in this area is required (40). A more recent evaluation (41) that used confocal microscopy to identify adenomatous-like lesions versus DALMs is encouraging for its sensitivity to differentiate these lesions. Unfortunately, confocal microscopy is presently not widely available.

METHODS TO ENHANCE DETECTION OF DYSPLASIA IN COLITIS

Random biopsy protocols have been documented to take longer than standard endoscopic procedures; ideally, methods to target biopsies could enhance the diagnostic yield while limiting the duration of the procedure. Both indigo carmine and methylene blue (42), combined with magnification endoscopy (43,44), have been shown in 'back-to-back' tandem endoscopies (conventional versus chromoendoscopy) to improve detection of dysplasia while limiting the number of biopsies.

Narrow band imaging (NBI) (45,46) has also been evaluated in a similar manner, with lesion patterns described (47). In a subsequent study that used both conventional endoscopy and NBI, the benefit was not realized – some lesions were recognized by the conventional method that were not recognized by NBI, thereby suggesting that both methods would have to be used for the procedure.

SUMMARY

There is an increased risk of colon cancer in patients with colitis, which affects both UC and CD. Biopsy protocols have been suggested at regular intervals to assess for findings of dysplasia. The assessment of dysplasia can be enhanced by the use of chromoendoscopy, which allows targeting the biopsies while increasing the diagnostic yield. Standard conventional white light biopsy continues to be the technique most commonly used; however, other imaging modalities such as NBI are gaining acceptance and further study may enhance our understanding of how to use them properly to maximize their benefit.

REFERENCES

- Blonski W, Kundu R, Furth EF, Lewis J, Abera F, Lichtenstein GR. High-grade dysplastic adenoma-like mass lesions are not an indication for colectomy in patients with ulcerative colitis. *Scand J Gastroenterol* 2008;43:817-20.
- Engelsgerd M, Farraye FA, Odze RD. Polypectomy may be adequate treatment for adenoma-like dysplastic lesions in chronic ulcerative colitis. *Gastroenterology* 1999;117:1288-94.
- Medlicott SA, Jewell LD, Price L, Fedorak RN, Sherbaniuk RW, Urbanski SJ. Conservative management of small adenomata in ulcerative colitis. *Am J Gastroenterol* 1997;92:2094-8.
- Farmer RG. Cancer risk in ulcerative colitis. *Scand J Gastroenterol* 1989;170(Suppl):75-7.
- Leidenius M, Kellokumpu I, Husa A, Riihela M, Sipponen P. Dysplasia and carcinoma in longstanding ulcerative colitis: An endoscopic and histological surveillance programme. *Gut* 1991;32:1521-5.
- Lennard-Jones JE, Melville DM, Morson BC, Ritchie JK, Williams CB. Precancer and cancer in extensive ulcerative colitis: Findings among 401 patients over 22 years. *Gut* 1990;31:800-6.
- Eaden JA, Mayberry JF. Guidelines for screening and surveillance of asymptomatic colorectal cancer in patients with inflammatory bowel disease. *Gut* 2002;51(Suppl 5):V10-V12.
- Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: A meta-analysis. *Gut* 2001;48:526-35.
- Rutter MD, Saunders BP, Wilkinson KH, Kamm MA, Williams CB, Forbes A. Most dysplasia in ulcerative colitis is visible at colonoscopy. *Gastrointest Endosc* 2004;60:334-9.
- Shetty K, Rybicki L, Brzezinski A, Carey WD, Lashner BA. The risk for cancer or dysplasia in ulcerative colitis patients with primary sclerosing cholangitis. *Am J Gastroenterol* 1999;94:1643-9.
- Soetikno RM, Lin OS, Heidenreich PA, Young HS, Blackstone MO. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis: A meta-analysis. *Gastrointest Endosc* 2002;56:48-54.
- Broome U, Bergquist A. Primary sclerosing cholangitis, inflammatory bowel disease, and colon cancer. *Semin Liver Dis* 2006;26:31-41.
- Vera A, Gunson BK, Ussatoff V, et al. Colorectal cancer in patients with inflammatory bowel disease after liver transplantation for primary sclerosing cholangitis. *Transplantation* 2003;75:1983-8.
- Friedman S, Rubin PH, Bodian C, Harpaz N, Present DH. Screening and surveillance colonoscopy in chronic Crohn's colitis: Results of a surveillance program spanning 25 years. *Clin Gastroenterol Hepatol* 2008;6:993-8.
- Canavan C, Abrams KR, Mayberry J. Meta-analysis: Colorectal and small bowel cancer risk in patients with Crohn's disease. *Aliment Pharmacol Ther* 2006;23:1097-1104.
- Itzkowitz SH, Present DH. Consensus conference: Colorectal cancer screening and surveillance in inflammatory bowel disease. *Inflamm Bowel Dis* 2005;11:314-21.
- Herszenyi L, Farinati F, Miheller P, Tulassay Z. Chemoprevention of colorectal cancer: Feasibility in everyday practice? *Eur J Cancer Prev* 2008;17:502-14.
- Carrier J, Medline A, Sohn KJ, et al. Effects of dietary folate on ulcerative colitis-associated colorectal carcinogenesis in the interleukin 2- and beta-2-microglobulin-deficient mice. *Cancer Epidemiol Biomarkers Prev* 2003;12:1262-7.
- Kelly GS. Folate: Supplemental forms and therapeutic applications. *Altern Med Rev* 1998;3:208-20.
- Lashner BA, Provencher KS, Seidner DL, Knesebeck A, Brzezinski A. The effect of folic acid supplementation on the risk for cancer or dysplasia in ulcerative colitis. *Gastroenterology* 1997;112:29-32.
- Sjovist U, Tribukait B, Ost A, Einarsson C, Oxelmark L, Lofberg R. Ursodeoxycholic acid treatment in IBD-patients with colorectal dysplasia and/or DNA-aneuploidy: A prospective, double-blind, randomized controlled pilot study. *Anticancer Res* 2004;24:3121-7.
- Wolf JM, Rybicki LA, Lashner BA. The impact of ursodeoxycholic acid on cancer, dysplasia and mortality in ulcerative colitis patients with primary sclerosing cholangitis. *Aliment Pharmacol Ther* 2005;22:783-8.
- Chu EC, Chai J, Ahluwalia A, Tarnawski AS. Mesalazine downregulates c-Myc in human colon cancer cells. A key to its chemopreventive action? *Aliment Pharmacol Ther* 2007;25:1443-9.
- Ullman T, Croog V, Harpaz N, Hossain S, Kornbluth A, Bodian C, Itzkowitz S. Progression to colorectal neoplasia in ulcerative colitis: Effect of mesalamine. *Clin Gastroenterol Hepatol* 2008;6:1225-30.
- Velayos FS, Terdiman JP, Walsh JM. Effect of 5-aminosalicylate use on colorectal cancer and dysplasia risk: A systematic review and meta-analysis of observational studies. *Am J Gastroenterol* 2005;100:1345-53.
- Bernstein CN, Weinstein WM, Levine DS, Shanahan F. Physicians' perceptions of dysplasia and approaches to surveillance colonoscopy in ulcerative colitis. *Am J Gastroenterol* 1995;90:2106-14.
- Eaden JA, Ward BA, Mayberry JF. How gastroenterologists screen for colonic cancer in ulcerative colitis: An analysis of performance. *Gastrointest Endosc* 2000;51:123-8.
- Farraye FA, Waye JD, Moscandrew M, Heeren TC, Odze RD. Variability in the diagnosis and management of adenoma-like and non-adenoma-like dysplasia-associated lesions or masses in inflammatory bowel disease: An Internet-based study. *Gastrointest Endosc* 2007;66:519-29.
- Blackstone MO, Riddell RH, Rogers BH, Levin B. Dysplasia-associated lesion or mass (DALM) detected by colonoscopy in long-standing ulcerative colitis: An indication for colectomy. *Gastroenterology* 1981;80:366-74.
- Lim CH, Dixon MF, Vail A, Forman D, Lynch DA, Axon AT. Ten-year follow up of ulcerative colitis patients with and without low grade dysplasia. *Gut* 2003;52:1127-32.
- Befrits R, Ljung T, Jaramillo E, Rubio C. Low-grade dysplasia in extensive, long-standing inflammatory bowel disease: A follow-up study. *Dis Colon Rectum* 2002;45:615-20.
- Rubin PH, Friedman S, Harpaz N, et al. Colonoscopic polypectomy in chronic colitis: Conservative management after endoscopic resection of dysplastic polyps. *Gastroenterology* 1999;117:12951300.
- Odze RD, Farraye FA, Hecht JL, Hornick JL. Long-term follow-up after polypectomy treatment for adenoma-like dysplastic lesions in ulcerative colitis. *Clin Gastroenterol Hepatol* 2004;2:534-41.
- Lovig T, Andersen SN, Clausen OP, Rognum TO. Microsatellite instability in long-standing ulcerative colitis. *Scand J Gastroenterol* 2007;42:586-91.
- Mahid SS, Minor KS, Brangers BC, Cobbs GA, Galandiuk S. SMAD2 and the relationship of colorectal cancer to inflammatory bowel disease. *Int J Biol Markers* 2008;23:169-75.
- Marx A, Wandrey T, Simon P, et al. Combined alpha-methylacyl coenzyme A racemase/p53 analysis to identify dysplasia in inflammatory bowel disease. *Hum Pathol* 2009;40:166-73.
- Nathanson JW, Yadron NE, Farnan J, Kinnear S, Hart J, Rubin DT. p53 mutations are associated with dysplasia and progression of dysplasia in patients with Crohn's disease. *Dig Dis Sci* 2008;53:47480.
- Weber CR, Nalle SC, Tretiakova M, Rubin DT, Turner JR. Claudin-1 and claudin-2 expression is elevated in inflammatory bowel disease and may contribute to early neoplastic transformation. *Lab Invest* 2008;88:1110-20.
- Yagishita H, Yoshida T, Ishiguro K, Numata Y, Okayasu I. Epithelial and stromal genetic instability linked to tumor suppressor genes in ulcerative colitis-associated tumorigenesis. *Scand J Gastroenterol* 2008;43:559-66.
- Fujiwara I, Yashiro M, Kubo N, Maeda K, Hirakawa K. Ulcerative colitis-associated colorectal cancer is frequently associated with the microsatellite instability pathway. *Dis Colon Rectum* 2008;51:1387-94.
- Hurlstone DP, Thomson M, Brown S, Tiffin N, Cross SS, Hunter MD. Confocal endomicroscopy in ulcerative colitis: differentiating dysplasia-associated lesion mass and adenoma-like mass. *Clin Gastroenterol Hepatol* 2007;5:1235-41.
- Sada M, Igarashi M, Yoshizawa S, et al. Dye spraying and magnifying endoscopy for dysplasia and cancer surveillance in ulcerative colitis. *Dis Colon Rectum* 2004;47:1816-23.
- Ando T, Takahashi H, Watanabe O, et al. Magnifying chromoscopy, a novel and useful technique for colonoscopy in ulcerative colitis. *World J Gastroenterol* 2007;13:2523-8.
- Rutter MD, Saunders BP, Schofield G, Forbes A, Price AB, Talbot IC. Pancolonic indigo carmine dye spraying for the detection of dysplasia in ulcerative colitis. *Gut* 2004;55:256-60.
- Dekker E, Fockens P. New imaging techniques at colonoscopy: Tissue spectroscopy and narrow band imaging. *Gastrointest Endosc Clin N Am* 2005;15:703-14.
- Overhiser AJ, Sharma P. Advances in endoscopic imaging: Narrow band imaging. *Rev Gastroenterol Disord* 2008;8:186-93.
- East JE, Suzuki N, von HA, Saunders BP. Narrow band imaging with magnification for dysplasia detection and pit pattern assessment in ulcerative colitis surveillance: A case with multiple dysplasia associated lesions or masses. *Gut* 2006;55:1432-5.