

Ulcerative Colitis – The Scope of Dysplasia

**Robert H. Riddell, MD FRCPC FRCPath
Mount Sinai Hospital, Toronto, Canada
Prof of Lab Medicine & Pathobiology
University of Toronto**

GIPS San Antonio Feb. 28, 2005

Ulcerative colitis (UC) is an inflammatory disease in which the risk of colorectal cancer is increased. The risk increases with extent of disease, including backwash ileitis which indicates total large bowel disease, length of history, early onset, activity of disease, family history of colorectal cancer and sclerosing cholangitis; the risk may be reduced with anti-inflammatory therapy. However, the problem that became apparent decades ago that patients with longstanding extensive disease would present with advanced and sometimes multiple colorectal cancer: the prognosis was correspondingly poor. Worse, the mean age of patients presenting with colitic cancers was in their early 40's, a time at which many had relatively young families, were developing their careers, and had heavy fiscal responsibilities. A major issue became how to prevent patients developing and dying from these carcinomas. Initially the only recourse was "prophylactic" total proctocolectomy, with an unwanted ileostomy or subsequently a pouch operation. A better marker of increased risk was required short of an invasive carcinoma the stage of which could not be accurately assessed.

While the concept of a pre-invasive lesion in colorectal cancer had long been recognized, the notion that adenomas preceded carcinomas was expounded in the 60's by Morson at St. Mark's Hospital in London England, and it became a logical step to consider that a similar principle applied to UC. Indeed, in patients undergoing resection for carcinoma in UC, widespread "dysplasia" (as it was called), was frequently found in patients undergoing resection for colitic cancers. The fact that the dysplasia was so widespread that the rectum was invariably involved led Morson and Pang(1) (1967) to suggest that regular rectal biopsies might well be able to detect rectal dysplasia, which in turn would identify patients at particularly high risk for the development of carcinoma. The era of trying to predict which patients within a high risk group might be particularly at risk was born.

An initial series of issues developed very quickly. Some patients with carcinoma clearly did not have widespread dysplasia (indeed, sometimes there was no dysplasia), nor did it involve the rectum, so rectal biopsies alone were clearly inadequate. Fortunately, the flexible sigmoidoscope, and then the full-length colonoscope were chronologically "just around the corner" so that it became possible to examine patients regularly and to take multiple biopsies in an

attempt to further refine patients at risk. This solved the issue of accessibility to the proximal colon but a second series of issues emerged:

- a) Some patients would be found with small (and sometimes large) tumors, occasionally when the previous colonoscopy had been negative. Thus the risk a lesion being invasive was quickly found to differ depending on whether it was found at the initial (screening) colonoscopy or a subsequent (surveillance) colonoscopy, a principle that still holds(2;3).
- b) Because on follow-up (surveillance) colonoscopy, some patients actually had carcinomas, surveillance colonoscopy was also a method of detecting small carcinomas (not necessarily “early” pathologically). Surveillance carcinoma therefore became a screen for both dysplasia and carcinoma.
- c) Patients were found with endoscopic abnormalities varying from mucosal irregularities, plaques, nodules or polypoid lesions which were dysplastic / adenomatous on biopsy. However if colectomy was carried out on these patients the abnormality was often found to harbor an underlying invasive carcinoma that was not suspected clinically. Worse, sometimes these lesions were advanced, and patients still died of their carcinoma, although this seemed to occur much more frequently when the endoscopic abnormality was found on the initial screening colonoscopy. This gave rise to the concept of “dysplasia-associated lesions or masses” (DALMs - Blackstone), which therefore became an indication for proctocolectomy(4).
- d) Patients with only dysplasia also had unexpected carcinomas found incidentally in colectomy specimens, especially if found on screening colonoscopy, so that the diagnosis of “dysplasia” became a potential indication for colectomy(5).

This became a major bone of contention, because there was no good agreement between pathologists as to what constituted “dysplasia”. It was recognized that in colectomy specimens and in biopsies, that nuclear features were encountered that were not normal but it was unclear whether they were also risk factors for carcinoma. Some were overtly occurring in inflamed mucosa. Because of the confusion that clearly existed, a slide exchange was arranged in the early 1980s in which any pathologist that had written about dysplasia in colitis was invited to participate. This resulted in the Human Pathology paper in 1983 that tried to address many of these issues(6). Issues that needed addressing urgently were

- a) the spectrum of reactive changes and their separation from dysplasia
- b) a definition of dysplasia
- c) a grading system for dysplasia
- d) implications of each of these “grades”

20 years ago the solutions to some of these were somewhat revolutionary. We were so uncertain about where reactive changes stopped and which were likely dysplastic that there was not only a “don’t know” category in the grading system – itself revolutionary – the acknowledgment that pathologists might “not know” was, at the time, one that pathologists (and the clinicians with whom they interacted), had problems accepting, as pathology was always taught to be “the final arbiter”, and were therefore not allowed “not to know”. There were also 3 grades of don’t know – which were more grades than there were for dysplasia itself. And just to rub it in, if you had any doubt about the ability of any specific type of epithelium to give rise directly to an invasive carcinoma, it could not be called dysplastic. The diagnosis of “indefinite for dysplasia” was therefore arrived at by asking 2 simple questions:

Is this epithelium unequivocally negative for dysplasia?

Is this epithelium unequivocally positive for dysplasia?

If the answer to both of these questions was “no” then one was dealing with “indefinite for dysplasia”.

The grading system: Although “mild, moderate and severe” was the grading system in common parlance at the time, a mere glance at the kappa values in the interobserver variability study made it clear that 2 were preferable, not only to improve kappa values, but because management could readily be tied in with a 2-grade system. Low and high grade dysplasia were thus introduced along with no dysplasia and indefinite for dysplasia. However, within the study, and not reflected by kappa values, were that pathologists clearly stratified themselves into a spectrum regarding interpretation of the same slide with a malignant group (who tended to err on the high side, a benign group, that were on average about a full grade below the malignant group, and an intermediate group, who tended to be in between both of the other groups. It became very easy to predict who would call what, once one had made up one’s own mind and then titrated oneself against everyone else. However it was also clear that while the “adenomatous” pathway appeared the best recognized, that there were other variants/pathways that were only recognized as neoplastic because carcinomas were overtly falling off of them. One of these we would now call “serrated”.

“Implications” also created a dilemma. The association of HGD with an associated invasive carcinoma was already apparent, but it was also clear that some carcinomas arose directly from LGD (or less). Yet given the interobserver agreement that we knew to be present, it was difficult to give an unequivocal recommendation to carry out “prophylactic” colectomy for LGD, especially as it overlapped with IFD, the natural history of which was unclear. Further, it also became clear that even amongst this group of interested pathologists, was the potential necessity for confirming a diagnosis of dysplasia. This was a tough one to swallow, but thought necessary – if the experts were having such a tough time agreeing, one could only imagine what might be called HGD, and therefore an implication of colectomy, at the more grass roots level. However, it had also

become apparent that some crypts that fed into actively regenerating mucosa could mimic HGD very closely.

In the 20 years that have passed, some of this has been seriously (and rightly questioned) while new problems and concepts have emerged:

The definition of dysplasia. (An unequivocally neoplastic proliferation). The notion that we actually know what is neoplastic initially sounds pretty arrogant, although most of the time with the adenomatous type of dysplasia, we are confident because we have seen carcinomas fall off of it directly. But if there is identical epithelium without carcinoma falling off of it, why does some have carcinoma falling off of it and others not? They must surely be different? We could interpret this in terms of molecular differences yet to be defined – the “invasion genes”. Nevertheless it remains subjective and really only applies satisfactorily to the adenomatous pathway. One of the problems is that there clearly are other pathways which may or may not use the traditional adenomatous pathway including those involving mismatch repair genes and serrations, in which traditional dysplasia may be only one option. Sometimes, invasive carcinomas appear to arise from epithelium that is not dysplastic in the conventional adenomatous sense; indeed sometimes there is very little nuclear atypicity. Such “minimal deviation” carcinomas are always problematic in trying to reconcile very bland morphology with the paradoxical invasive pattern, which can be highly aggressive. There will always be the need for “better markers” of neoplasia, but it may be some time before we arrive at a the molecular diagnosis that must necessarily involve not only the epithelium but the host reactions including inflammatory and desmoplastic responses and the interchange of growth and suppression factors, some of which may be mutant, that occur between them.

The Vienna Classification for Dysplasia The classification system for dysplasia has remained virtually unchanged for since 1983, In 1998 an upgraded system was developed that it was hoped would help resolve international differences in terminology(7). It utilized the term “non-invasive neoplasia” – both low grade and high grade, and also borrowed the term “suspicious of invasive carcinoma for those tumors that have all of the hallmarks of invasion except that the invasive component cannot be demonstrated unequivocally. The re-introduction of the term carcinoma in situ was more for molecular work, as increasingly molecular work needs something between usual high grade dysplasia as defined by marked nuclear stratification and the architectural abnormalities that tend to be involved in carcinoma in situ. It is now used widely in Europe and frequently when those in other non-English speaking countries such as Japan publish in English journals. Like the original classification it also has management implications.

Reproducibility and need for a second opinion. All of the studies with dysplasia show a considerable and disturbing interobserver variability. Given

that potential colectomy with its morbidity and even mortality are on the line on one side, and possibly dying from a carcinoma if colectomy is not carried out in a timely manner, “getting it right” is important. Surprisingly, the impetus for suggesting a second opinion came from some of the comments made regarding how one arrived at a diagnosis of dysplasia, which were at times little more than tossing a coin. This has evolved to the point that the adenomatous pattern of dysplasia is fairly easy to diagnose in the absence of inflammation, although when maturation is present it can cause problems (in Barrett’s the existence of bottom up dysplasia is pretty well denied in one paper as it is a criterion for “indefinite for dysplasia”(8). While most dysplasia is maximal at the surface (top down dysplasia), a small proportion is maximal at the base with some degree of maturation (bottom up dysplasia). Because maturation is a feature of regeneration the differential diagnosis of maturation include both regeneration and bottom-up dysplasia. If maturation is used as the sine que non of regenerative changes, it follows that the existence of bottom up dysplasia is called into question, and virtually cannot exist, even though in some patients maturing dysplasia has infiltration from the base, as seen in for example, in a villous adenoma in the large bowel with invasive carcinoma, and also the superficial dysplastic component of many colloid cancers.

Vienna classification of GI epithelial neoplasia		
Category	Diagnosis	Management
Category 1	Negative for neoplasia/dysplasia	Optional
	Follow-up	
Category 2	Indefinite for neoplasia/dysplasia	Follow-up
Category 3	Non-invasive low grade neoplasia	Local Rx or
	Follow-up	
	(low grade adenoma/dysplasia)	
Category 4	Non-invasive high grade neoplasia	Local Rx
	4.1 High grade adenoma/dysplasia	
	4.2 Non-invasive carcinoma (carcinoma in situ)*	
	4.3 Suspicion of invasive carcinoma	
Category 5	Invasive neoplasia	Needs Rx
	5.1 Intramucosal carcinoma_	
	5.2 Submucosal carcinoma or beyond	

*** Non-invasive indicates absence of evident invasion. Intramucosal indicates invasion into the lamina propria or muscularis mucosae.**

There is increasing evidence that indefinite for dysplasia (IFD) in ulcerative colitis is at increased risk of developing subsequent invasive carcinoma than patients without dysplasia, and is may approximate that of LGD(2;9). As such it is important to appreciate that, while currently IFD is not an indication for endoscopic or surgical therapy, that it warrants careful follow up to ensure that LGD (or worse) is not present while follow-up should be ensured.

Dysplastic Polyps in UC This is the single most common problem in the management of colitics and our clinical colleagues (and some pathologists) seem to spend a lot of unnecessary time worrying about the ability to reliably distinguish apparently sporadic adenomas from dysplasia-associated lesions or masses (DALMs). As there is no reliable way to do this there are numerous algorithms available for managing this problem. However, the easiest guidelines are simplistically stated as follows

- a) Adenoma-like masses (ALMs) above the upper limit of disease can be regarded as sporadic adenomas and treated as such. (10;11)
- b) Dysplastic lesions within colitic mucosa can also be treated as sporadic adenomas provided they (i) can be demonstrably completely excised endoscopically (this means demonstrating a dysplasia free margin and no dysplasia in the immediately surrounding mucosa, (ii) can be shown to be unassociated with dysplasia elsewhere in the bowel (iii) the patient is in the adenoma bearing age range (often regarded to be <40 although these are not uncommon in the colitic population. If any of these provisos cannot be satisfied, serious consideration must be given to proctocolectomy. In practice, if the endoscopic appearance is suspicious of an invasive neoplasm some surgeons will proceed directly to proctocolectomy. Fears that one is dealing with an invasive lesion are often well founded.

Advances in detection of dysplasia

- a) **Pathology.** There have been numerous attempts to find a gold standard to replace light microscopy. These have involved detection of aneuploidy, p53, oncogenes such as K-ras, mismatch repair genes and increasingly other cell cycle markers, telomere length and also the whole notion that the mucosa in which dysplasia arises is not normal but has abnormalities that are detectable (12-18) Attention has also shifted from detecting changes in dysplastic mucosa to the surrounding non-neoplastic mucosa, which are clearly demonstrable particularly when looking at chromosomal instability including telomere shortening. Indeed in one study loss of 4 genes in non-dysplastic mucosa were shown to accurately predict which patients had carcinoma. It seems a matter of time before better predictors are found, but we have been saying that for a long time
- b) **Endoscopy and Biopsies.** There has been a lot of attention to the number of biopsies that are required, and looking for small areas of dysplasia is like looking for a needle in the proverbial haystack.

Further, if it is found, the notion of then trying to confirm it seems farcical. Detecting a 2cm patch of dysplasia (radius 1cm) means it has an area of 3.142cm^2 so that in a colon 100cm long and 10cm wide (1000cm^2) would require $1000/3.142$ biopsies (318!!!) while a33 are required to provide about a 90% chance of picking it up experimentally(13). Random biopsies will therefore always cause problems while even getting many endoscopists to take 30+ biopsies, and telling them that less than this is an inadequate series is a major problem.

The answer therefore also has to involve advances in colonoscopic techniques. It is increasingly apparent that most dysplasia does have an endoscopic abnormality of some sort,(19) although the introduction of magnification endoscopy and chromoscopy increasingly allows identification of pit patterns that may indicate dysplasia, apart from just exaggerating lesions detected colonoscopically.(20-25). The addition of additional endoscopic techniques such as narrow band imaging and high resolution colonoscopes accompanied by high resolution monitors are likely to make recognition of small areas of dysplasia very feasible given the huge increase in resolution that these scopes produce.

In summary, the whole story of evolution in colitis continues to evolve, and the pessimism that surveillance is expensive, does not work, and neither prevents the development of carcinoma or improves life expectancy can be seriously challenged.

Reference List

- (1) Morson BC, Pang LSC. Rectal biopsy as an aid to cancer control in ulcerative colitis. *Gut* 1967;8:423-434
- (2) Bernstein CN, Shanahan F, Weinstein WM. Are we telling patients the truth about surveillance colonoscopy in ulcerative colitis? *Lancet* 1994; 343(8889):71-74.
- (3) Lennard-Jones JE, Morson BC, Ritchie JK, Williams CB. Cancer surveillance in ulcerative colitis. Experience over 15 years. *Lancet* 1983; 2(8342):149-152.
- (4) 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(2):366-374.
- (5) Bernstein CN, Shanahan F, Weinstein WM. Are we telling patients the truth about surveillance colonoscopy in ulcerative colitis? *Lancet* 1994; 343:71-74.

- (6) Riddell RH, Goldman H, Ransohoff DF, Appelman HD, Fenoglio CM, Haggitt RC et al. Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. *Hum Pathol* 1983; 14(11):931-968.
- (7) Schlemper RJ, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM et al. The Vienna classification of gastrointestinal epithelial neoplasia. *Gut* 2000; 47(2):251-255.
- (8) Montgomery E, Goldblum JR, Greenson JK, Haber MM, Lamps LW, Lauwers GY et al. Dysplasia as a predictive marker for invasive carcinoma in Barrett esophagus: a follow-up study based on 138 cases from a diagnostic variability study. *Hum Pathol* 2001; 32(4):379-388.
- (9) Ullman T, Croog V, Harpaz N, Sachar D, Itzkowitz S. Progression of flat low-grade dysplasia to advanced neoplasia in patients with ulcerative colitis. *Gastroenterology* 2003; 125(5):1311-1319.
- (10) Bernstein CN. Ulcerative colitis with low-grade dysplasia. *Gastroenterology* 2004; 127(3):950-956.
- (11) 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(7):534-541.
- (12) O'Sullivan JN, Finley JC, Risques RA, Shen WT, Gollahon KA, Moskovitz AH et al. Telomere length assessment in tissue sections by quantitative FISH: image analysis algorithms. *Cytometry A* 2004; 58A(2):120-131.
- (13) Rubin CE, Haggitt RC, Burmer GC, Brentnall TA, Stevens AC, Levine DS et al. DNA aneuploidy in colonic biopsies predicts future development of dysplasia in ulcerative colitis. *Gastroenterology* 1992; 103(5):1611-1620.
- (14) Burmer GC, Levine DS, Kulander BG, Haggitt RC, Rubin CE, Rabinovitch PS. c-Ki-ras mutations in chronic ulcerative colitis and sporadic colon carcinoma. *Gastroenterology* 1990; 99(2):416-420.
- (15) Issa JP, Ahuja N, Toyota M, Bronner MP, Brentnall TA. Accelerated age-related CpG island methylation in ulcerative colitis. *Cancer Res* 2001; 61(9):3573-3577.
- (16) Rabinovitch PS, Dziadon S, Brentnall TA, Emond MJ, Crispin DA, Haggitt RC et al. Pancolonial chromosomal instability precedes dysplasia and cancer in ulcerative colitis. *Cancer Res* 1999; 59(20):5148-5153.
- (17) Brentnall TA, Crispin DA, Bronner MP, Cherian SP, Hueffed M, Rabinovitch PS et al. Microsatellite instability in nonneoplastic mucosa from patients with chronic ulcerative colitis. *Cancer Res* 1996; 56(6):1237-1240.

- (18) Brentnall TA, Crispin DA, Rabinovitch PS, Haggitt RC, Rubin CE, Stevens AC et al. Mutations in the p53 gene: an early marker of neoplastic progression in ulcerative colitis. *Gastroenterology* 1994; 107(2):369-378.
- (19) 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(3):334-339.
- (20) Fefferman DS, Farrell RJ. Endoscopy in inflammatory bowel disease: indications, surveillance, and use in clinical practice. *Clin Gastroenterol Hepatol* 2005; 3(1):11-24.
- (21) Mpofu C, Watson AJ, Rhodes JM. Strategies for detecting colon cancer and/or dysplasia in patients with inflammatory bowel disease. *Cochrane Database Syst Rev* 2004;(2):CD000279.
- (22) Rutter M, Bernstein C, Matsumoto T, Kiesslich R, Neurath M. Endoscopic appearance of dysplasia in ulcerative colitis and the role of staining. *Endoscopy* 2004; 36(12):1109-1114.
- (23) 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; 53(2):256-260.
- (24) 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(5):615-620.
- (25) Jaramillo E, Watanabe M, Befrits R, Ponce dL, Rubio C, Slezak P. Small, flat colorectal neoplasias in long-standing ulcerative colitis detected by high-resolution electronic video endoscopy. *Gastrointest Endosc* 1996; 44(1):15-22.