

# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

Section Editor: Stephen B. Hanauer, MD

---

## Low-Grade Colorectal Dysplasia and the Need for Colectomy

Thomas A. Ullman, MD  
Assistant Professor  
Division of Gastroenterology  
The Mount Sinai School of Medicine

### **G&H** What is the standard approach to stratifying IBD patients for risk of dysplasia and cancer?

**TU** Patients with longstanding ulcerative colitis (UC) or Crohn's disease, usually defined as 8–10 years of disease or more, involving at least one third of the colon, are at an increased risk for the development of colorectal cancer (CRC). Additional risk factors for CRC in colitis include a diagnosis of sclerosing cholangitis, a family history of colon cancer, and, in some studies, an early age of onset of colitis. More recently there has been interest in determining whether histologic inflammation is an independent risk factor for CRC. A group from St. Mark's Hospital in the United Kingdom performed a case-control study that supported the hypothesis that increased inflammation results in an increased risk for dysplasia and cancer. Our group at Mount Sinai found a similar relationship in a retrospective cohort study, and Dr. David Rubin and his colleagues at the University of Chicago recently reported on a similar association in a case-control study.

### **G&H** How are IBD-related cancers different from other forms of CRC?

**TU** Although there are molecular and morphologic similarities between sporadic CRC and IBD- or colitis-associated cancers, they are different in how they present in the colon. In sporadic CRC, there is typically a precursor lesion, which is an adenoma or precancerous polyp. Although raised lesions are common in colitis-associated cancers, many dysplastic precursors are not apparent to the eye of the endoscopist, and are found only in the sampling of colitis-associated mucosa. This is the reason for non-

targeted sampling of the colon in colitis dysplasia surveillance. Additionally, as multiple cancers are more frequent in colitis-associated cancers, we tend to think of the entire colorectum as being at risk when a single focus of dysplasia or cancer is detected. In fact, the original descriptions of dysplasia in colitis-associated CRC were found in the rectum of patients in whom CRC was present at a different site. This is what is meant by a "field effect" in colitis-associated cancers. Finally, the timing from colitis to dysplasia to carcinoma is less predictable and on average more rapid than that of sporadic colorectal cancer. This is the reason that experts recommend surveillance colonoscopies every 1–2 years in patients with colitis as opposed to every 5 years for patients with sporadic polyps.

### **G&H** What are the issues that impair the reliability of colonoscopic screening for IBD-related CRC?

**TU** One essential problem with colonoscopic surveillance is our complete dependence on pathology to accurately determine the presence of dysplasia or cancer in the setting of chronic inflammation. Even among expert pathologists, levels of agreement in interpreting dysplasia surveillance specimens are far from ideal. Other issues include the notion that dysplasia can be patchy, so under-sampling of the colonic surface area can be suboptimal for excluding the presence of dysplasia. If dysplasia is only in one or even several places, it can be very difficult to find unless large numbers of biopsies are performed.

Furthermore, as mentioned before in comparison to sporadic CRC, the natural history of progression from colitis to dysplasia to cancer is not well understood. We believe that we have an idea, in sporadic CRC, regarding how long it takes to get from normal tissue to an adenoma that is visible and can be removed, and for most adenomas to progress to cancer. We have a much more limited understanding of that same process as it applies to changes in colitis-associated CRC. Finally, there is the issue of doctor and patient adherence to a schedule of surveillance. Patients can miss an examination for any num-

ber of reasons, and doctors may forget to remind them. Sadly, there are many examples in the gastroenterologic literature in which such a lack of adherence has resulted in substantial morbidity and mortality.

With the combination of all of these factors, cancers can arise in cases where there has been no previous detection of dysplasia. Patients can be undergoing appropriate surveillance and cancer can still appear, despite the fact that they may have had a negative or normal surveillance examination a year previously.

### **G&H** Can you discuss the historic research on IBD-related CRC that has led to current practice protocols?

**TU** The initial surveillance paradigm was an outgrowth of the 1967 discovery that rectal dysplasia was associated with CRC in other sites and the subsequent advent of fiber optic colonoscopy. Patients and clinicians then had a third path that made both prophylactic colectomy and watchful waiting obsolete methods for cancer prevention in UC. Surveillance programs sprung up in multiple areas around the globe, and their collective experiences, as well as the application of modern population-based epidemiology, resulted in the rapid evolution of surveillance practices. The timing of onset, the identification of appropriate at-risk subgroups, the frequency of surveillance examinations, and the understanding that high-grade or severe dysplasia warranted a colectomy were established by the early 1980s, all without a clear mortality benefit demonstrated.

### **G&H** Have recommendations of surveillance practices changed in the last two decades?

**TU** By the time these strategies matured in the early 1980s, Dr. Robert Riddell and other researchers came together and developed codified definitions of all levels of dysplasia in colitis. Although Esperanto failed, it was recognized that standards across countries and continents were needed. It is worth noting that prior to the establishment of these definitions, low-grade or mild dysplasia, although undefined, was thought to carry a low to negligible risk for imminent CRC in colitis. However, in 1994, Dr. William Connell and his group at St. Mark's Hospital completed an analysis of their patients utilizing the new definitions. They found that among their patients with low-grade dysplasia, previously thought to be fairly innocuous, 54% progressed to high-grade dysplasia or cancer at 5 years. In the same year, Dr. Charles Bernstein completed a systematic review of all the then-published literature of surveillance programs worldwide, and found that among patients with low-grade dysplasia who under-

went immediate colectomy, 3 of 16 (19%) had cancer when their colons were removed and examined. With the publication of these two studies, the pendulum of opinion swung to the idea that low-grade dysplasia was something considerably more dangerous than originally thought.

In 1999 when I was at the Mayo Clinic, our group looked, retrospectively, at 18 patients who had low-grade dysplasia and found that one of them went on to develop a lethal cancer and fully one third developed high-grade dysplasia or cancer at 5 years in an actuarial model. This seemed to confirm what Connell had found at St. Mark's. I then followed up these findings here at Mt. Sinai. We had 46 patients with flat low-grade dysplasia detected via untargeted biopsies. We postulated that among these cases, those with one positive finding of low-grade dysplasia, as opposed to multiple findings, could be classified as a lower-risk group, with clear separation in terms of likelihood of progression. What we found was that there was no separation at all. Both unifocal and multifocal low-grade dysplasia progressed to high-grade dysplasia or CRC at a rate close to 50% at 5 years. Additionally, 20% of patients who had surgery for low-grade dysplasia without any other finding, had cancer upon in-depth examination at the time of their colectomy, confirming Bernstein's findings. Most worrisome, we identified 3 patients who continued with surveillance and developed node-positive cancer despite no evidence of progression beyond low-grade dysplasia prior to the discovery of CRC. Of those three, two had undergone multiple surveillance examinations, including dysplasia-free examinations within 12 months of the discovery of CRC. These findings suggested that although surveillance may be effective in a population of patients with longstanding UC, it probably was not safe in patients after they had a finding of low-grade dysplasia, even if that finding was only in one site.

At the same time, another group here at Mt. Sinai, under the leadership of Dr. Peter Rubin, and a group from Boston, under the pathologist Dr. Robert Odze, published their experience with polypoid dysplasia in chronic colitis. They postulated that small adenoma-like lesions with dysplasia that could be easily resected could be treated as adenomas. In the Rubin study, when the lesions were resected and biopsies performed in the areas adjacent to the polypectomy site, none of the patients progressed to more advanced pathology. Initial and follow-up studies by Odze and colleagues were encouraging also, although one patient progressed to CRC, albeit a number of years after the adenoma finding. Additionally, a recent publication by Rutter and associates confirmed much of these findings. In the setting of low-grade dysplasia that was not polypoid, their group found that 25% of patients developed high-grade dysplasia or cancer within 5 years. In the polypoid CRC group, they were able to

successfully remove adenomas in a manner similar to the Rubin and Odze groups, and found that progression was halted. Our pathologist at Mt. Sinai, Dr. Noam Harpaz, published a study in 2006 looking at resected specimens of low-grade tubuloglandular adenocarcinoma, which were in effect low-grade dysplasia on the surface with an adenocarcinoma lesion lurking below. This is a dangerous phenomenon that further adds, in my opinion, to the wisdom of removing the colon for flat, or incompletely resected low-grade dysplasia.

### **G&H** Are there any published data that contradict these findings?

**TU** There are several studies, chief of which is from a group at the Karolinska Institute led by Befrits, where only 2% of patients with findings of flat low-grade dysplasia developed advanced pathology in 10 years. However, this group did not use the conventional Riddell criteria. In their group, patients with indefinite dysplasia were included because a reading of “indefinite” was not allowed as an option at their institution. Similarly a group from Leeds, UK, led by Anthony Axon, who has been a critic of surveillance as a cancer prevention strategy, found that only 10% of their patients had more advanced pathology at 10 years, among a group of 29 patients.

### **G&H** How do you present all of this information to your IBD patients and help them to make decisions in terms of their course of treatment?

**TU** In discussing the question of surgery with IBD patients who have a finding of low-grade dysplasia, I present it as a question of probabilities for them to solve. I explain that if our pathologists have confirmed the presence of flat low-grade dysplasia, they have a 20% chance of already having a cancer and anywhere from a 25% to a 50% chance of progressing to high-grade dysplasia or cancer in 5 years. I additionally tell them that there is the possibility that even with surveillance, there may be no sign of progression until a lymph-node positive cancer appears. Finally, I discuss with them what life with a J-pouch will likely entail. With this information in hand, patients then make their own assessment of the risks and decide what is acceptable in exchange for avoidance of colectomy.

### **G&H** Are there any emerging diagnostic or therapeutic modalities that can be offered to patients as hope for a better future prognosis?

**TU** Chromoendoscopy with methylene blue or indigo carmine dye and narrow band imaging are two new endo-

scopic techniques that are being utilized experimentally to augment or highlight surface features and almost certainly improve dysplasia detection. Investigations of these techniques have been performed by Drs. Rolf Keisslich and Matthew Rutter and are quite convincing. Unfortunately, everything we know, or think we know, about the natural history of dysplasia and subsequent risk for CRC may prove useless when our methods for dysplasia detection improve in accuracy. Obviously, though, that is a risk worth taking.

With regard to medical therapies, there is some circumstantial evidence supporting the notion that colitis-related CRC is not as prevalent as it once was and that the mesalamine-based agents, currently used to treat active UC and maintain remissions, are chemopreventive. However, with the detection of dysplasia, the chemopreventive attributes of mesalamine do not seem to halt or retard progression or have any effect on subsequent risk. Ursodeoxycholic acid is chemopreventive in sclerosing cholangitis-related UC cancer. There is suggestive, but less compelling, evidence that folic acid is chemopreventive.

### **Suggested Reading**

- 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;45:615-620.
- Bernstein CN, Weinstein WM, Levine DS, Shanahan F. Physicians' perceptions of dysplasia and approaches to surveillance colonoscopy in ulcerative colitis. *Am J Gastroenterol*. 1995;90:2106-2114.
- Bernstein CN, Shanahan F, Weinstein WM. Are we telling patients the truth about surveillance colonoscopy in ulcerative colitis? *Lancet*. 1994;343:71-74.
- Connell WR, Lennard-Jones JE, Williams CB, et al. Factors affecting the outcome of endoscopic surveillance for cancer in ulcerative colitis. *Gastroenterology*. 1994;107:934-944.
- 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; discussion 1488-1491.
- Kiesslich R, Fritsch J, Holtmann M, et al. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. *Gastroenterology*. 2003;124:880-888.
- Lim CH, Dixon MF, Vail A, et al. Ten year follow up of ulcerative colitis patients with and without low grade dysplasia. *Gut*. 2003;52:1127-1132.
- Riddell RH, Goldman H, Ransohoff DF, et al. Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. *Hum Pathol*. 1983;14:931-968.
- Rubin PH, Friedman S, Harpaz N, et al. Colonoscopic polypectomy in chronic colitis: conservative management after endoscopic resection of dysplastic polyps. *Gastroenterology*. 1999;117:1295-1300.
- Rutter M, Saunders B, Wilkinson K, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology*. 2004;126:451-459.
- Rutter MD, Saunders BP, Schofield G, et al. Pancolonic indigo carmine dye spraying for the detection of dysplasia in ulcerative colitis. *Gut*. 2004;53:256-260.
- Ullman TA, Loftus EV Jr, Kakar S, et al. The fate of low grade dysplasia in ulcerative colitis. *Am J Gastroenterol*. 2002;97:922-927.
- Ullman T, Croog V, Harpaz N, et al. Progression of flat low-grade dysplasia to advanced neoplasia in patients with ulcerative colitis. *Gastroenterology*. 2003;125:1311-1319.