Colon Cancer in IBD: A Paradigm for the Role of Inflammation in Neoplastic Development

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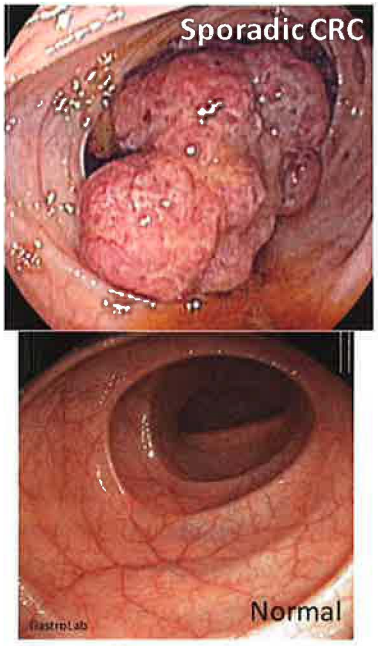
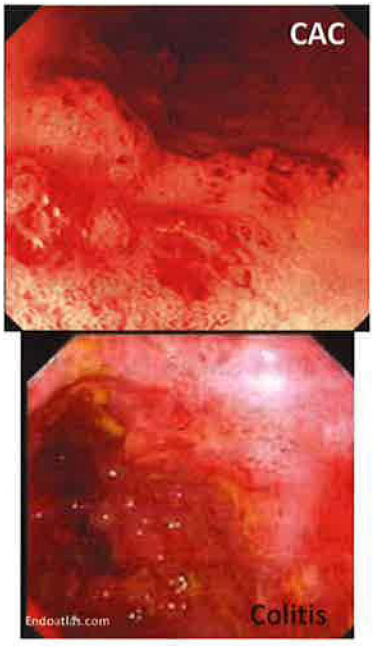


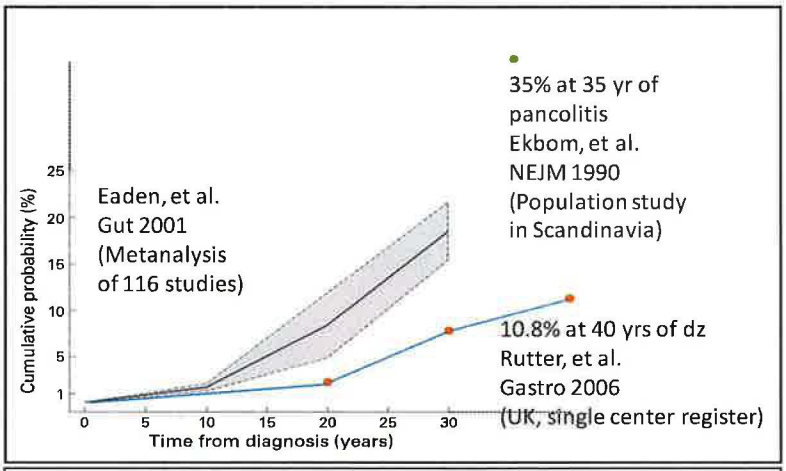


Patients with inflammatory bowel disease (IBD) are known to have an increased risk for colorectal cancer (CRC). This form of cancer has been referred to as colitis-associated cancer (CAC) and in this lecture I will review the main aspects of the epidemiology of this process, its pathophysiology and what it teaches us regarding the role of inflammation on cancer development. Finally, at the end of the talk I will discuss surveillance recommendations for early detection of dysplasia and malignancy.

Epidemiology

Colon cancer is the second most common cause of cancer mortality in the United States. The lifetime risk of colorectal cancer in the general population is approximately 5%. To put this figure in context, the lifetime risk of any invasive cancer is 44% for males and 38% for females. Colorectal cancer is largely divided between two categories, sporadic cancer and familial forms of colorectal cancer. There are various familial syndromes that can give rise to CRC but the main two syndromes are hereditary non-polyposis colon cancer or HNPCC and familial adenomatous polyposis or FAP. Familial cases contribute approximately 10% of all CRC, while colorectal cancer in IBD patients contributes only about 1% of all colon cancers. Even though the contributions of IBD to colon cancer morbidity is relatively small CAC represents the second most common cause of disease related mortality in IBD patients. Therefore, for this patient population, CAC represents a significance source of complications and mortality.

CAC was first recognized by Crohn and Rosenberg in 1925 as a complication in a patient with ulcerative colitis. This initial observation has been since replicated in multiple populations, in various continents and ethnic backgrounds. In addition, the initial clinical observation that was made in patients with ulcerative colitis has since been extended to patients with Crohn's Disease. The various studies available in the literature report a magnitude of the risk that is variable, and recent studies suggest that this complication may be decreasing with time. A large metanalysis performed by Eaden and colleagues in 2001, in which 116 previous studies with over 50,000 patients with ulcerative colitis were included, demonstrated an overall risk of cancer of 18% at 30 years. In contrast a large single center register in the United Kingdom found lower rates of CAC in their IBD population. In particular the rate of cancer was reported to be 10.8% at 40 years of disease diagnosis. On the other extreme the reported cancer risk is a study by Ekbom and colleagues. This large population-based study in Scandinavia reported a 35% probability of cancer in patients with pancolitis for over 35 years. In contrast to the studies that I just referred to, some notable exceptions reported no increase risk in cancer in patients with IBD. In particular, a recent population-based study in Olmstead County, Minnesota did not find an increase risk of colorectal cancer in patients with IBD. However, the development of dysplasia and the need for colectomy was not reported in this study. Despite these exceptions, it is largely accepted that there is an increased risk of cancer in patients with long-standing IBD.

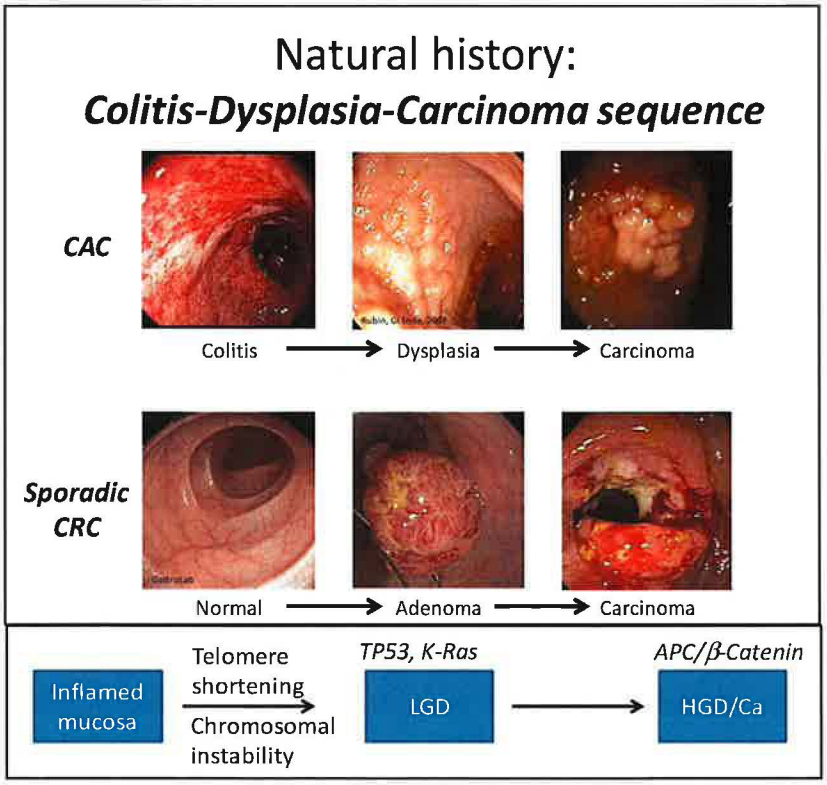


Risk of CAC over time in three representative studies

Natural history and genetics of CAC

Chronic inflammation gives rise initially to a non-invasive neoplastic change referred to as dysplasia, from which invasive tumors arise. This colitis-dysplasia-cancer sequence is analogous to the adenoma-carcinoma sequence described in sporadic CRC. In fact, the rise in cancer risk in colitis patients is primarily observed after the first decade of inflammation, consistent with the timeframe for adenoma-carcinoma progression. Moreover, like sporadic CRC, CAC is

a chromosomally unstable tumor that demonstrates high degree of aneuploidy. Telomere shortening and chromosomal instability with chromosomal arm losses can be detected in non-dysplastic mucosa of patients with dysplasia or cancer elsewhere. This finding attests to the fact that the genomic alterations that give rise to neoplasia occur diffusely throughout the colonic mucosa and can be detected molecularly prior to histologic changes. Recurrent chromosomal abnormalities seen in CAC are also found in sporadic cancer, but the number of chromosomal alterations in inflammatory tumors is reportedly greater.



Our understanding of the genetic lesions that give rise to these tumors is limited and studies with modern genomic techniques are few. Unlike sporadic CRC development, which is marked by early mutations in APC or other factors in the Wnt pathway that control nuclear β-Catenin accumulation, APC/β-Catenin abnormalities are uncommon in low grade dysplasia. Conversely, mutations in the tumor suppressor p53 are commonly found in low grade dysplasia or even histologically normal epithelium, while they are rather seen in advanced invasive sporadic cancers and seldom are present at the adenoma stage. Despite these two differences, the genetics of CAC are largely untapped and very few examples of cancer cell lines derived from this type of tumors are available.

The finding that non-dysplastic mucosa can display aneuploidy and mutations in p53, has generated the notion that there is broad mutagenic damage extending widely across the colonic mucosa of these patients. This hypothesis of a field effect is also consistent with the observation that dysplasia can be frequently associated with other neoplastic changes (additional dysplasia or cancer) in other areas of the colon. Direct testing of this field hypothesis was performed by Salk and colleagues. Using the length of polyguanidine stretches as a marker of mutagenic damage, the authors found that non-dysplastic mucosa demonstrated frequent evidence of genetic alterations in patients with colitis that had concurrent cancer or high grade dysplasia elsewhe in the colon, and not in colitis patients without dysplasia. Using this type of approach it was also evident that genetic alterations were widespread within the colon not only involving the region where cancer or high grade dysplasia was noted, but also in adjacent and distant areas. Altogether, this line of evidence has generalized the notion that cancer in patients with colitis is the end result of a broad mutagenic insult that spans most of the patient's colon. This consideration is important to bear in mind when considering therapeutic approaches to the diagnosis of dysplasia in these patients.

Risk factors for CAC

–Early onset of disease

- 40% risk for CAC at 35 yr for pts dx'd before 15 yo (Ekbom et al, NEJM, 1990)

–Severe inflammation

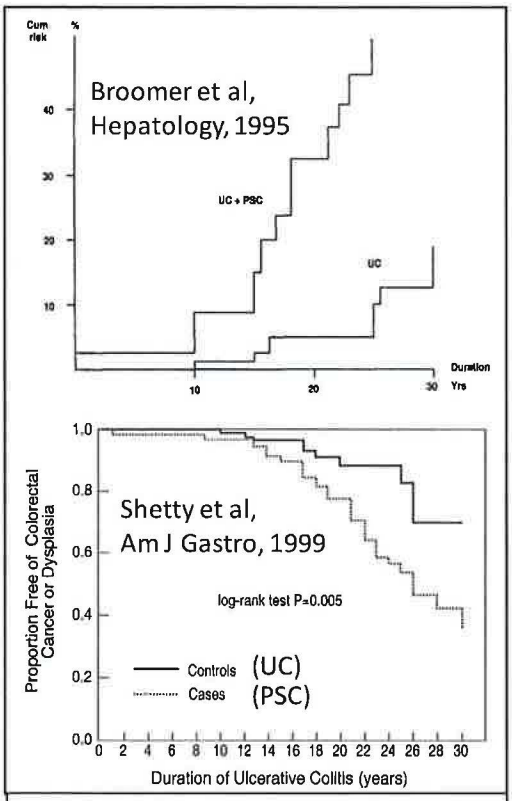
- Histologic or endoscopic severity correlates with CAC risk (Gupta, Gastroenterology, 2007)
- Colon shortening
- Pseudopolyps

–Extensive inflammation

- Highest risk for pancolitis, next for L sided colitis, no increased risk for proctitis (Ekbom et al)
- 'Backwash ileitis' also reported to have increased risk (Heuschen, Gastro, 2001)

Risk factors for CAC

The epidemiology of CAC has revealed a number of risk factors that are associated with the development of this complication. One such risk factor is a diagnosis of colitis at an early age. This has been observed repeatedly in a variety of studies including the report by Ekbom, which found a 40% risk of CAC at 35 years of diagnosis for patients whose disease began before the age of 15. Other reported risk factors for CAC are severe inflammation and extensive inflammation. While severity is difficult to quantify, retrospective analyses of endoscopic or histologic severity assessments identified that severity of inflammation is predictive of CAC development. Similarly, colonic shortening and pseudopolyps, which develop as a consequence of severe inflammation, have both been reported to be associated with a higher risk of cancer development. With regards to the extent of inflammation, the highest risk for CAC is observed in patients with pancolitis, followed by patients with left-sided colitis. On the other hand, most studies report no increased risk for patients who have disease restricted to the rectum. Backwash ileitis, a form of ileal inflammation observed in patients with extensive and severe ulcerative pancolitis has also been reported to be associated with an increased risk of colorectal cancer.



Risk of CAC in 2 representative studies of PSC

Among the various risk factors for CAC, one of the most dominant is the concomitant presence of Primary Sclerosing Cholangitis (PSC). This disorder is seen in 2-6% of patients with colitis and is characterized by inflammatory and fibrotic changes in the biliary tree that lead to chronic strictures, cholestasis, secondary biliary cirrhosis and a high risk for cholangiocarcinoma. PSC is a male predominant disorder, usually of early onset. Most patients with PSC have evidence of colitis endoscopically and histologically, even though some of them may be asymptomatic. In fact, the degree of inflammation tends to be less severe than in UC patients in general, although the anatomic involvement is generally extensive. The increase risk of cancer in this population has been reported repeatedly since 1995. Although the cohorts of patients described are all small, there has been a uniformly striking increase in the risk of cancer for patients with PSC and colitis, compared to patients with UC. For example, a cohort from Scandinavia reported by Broomer developed colon cancer in nearly 50% of cases by 25 years of follow up and similar findings were made in the United States by Shetty.

Cancer and Inflammation: a relationship that extends beyond CAC

The epidemiological data we just reviewed indicate clearly that inflammation itself plays a critical role in the risk for cancer development in patients with colitis. Moreover, in addition to this relationship in IBD, multiple examples of inflammation-associated cancers have been indentified in other organs. In the digestive tract alone esophageal carcinoma, gastric cancer, and small intestine adenocarcinoma, have a higher risk of developing risk in the setting of various inflammatory disorders. The same is true of cholangiocarcinoma whose risk is increased by PSC

ORGAN	*INFLAMMATORY PROCESS*	*TUMOR*
• Esophagus	GERD	Esophageal adenoCa
• Stomach	Chronic gastritis (*H. pylori*)	Gastric cancer
• Small Intestine	Celiac disease; Crohn's disease	Small intestinal AdenoCa
• Biliary Tree	PSC, liver fluke infection	Cholangiocarcinoma
• Pancreas	Chronic pancreatitis	Pancreatic cancer
• Liver	Chronic hepatitis	Hepatocellular carcinoma
• Bladder	Schistosomiasis	Squamous cell Ca
• Lung	Tobacco/chronic bronchitis	Lung Ca

Evidence of smoldering inflammation in the form of an inflammatory infiltrate and cytokine production is nearly universally seen in cancer

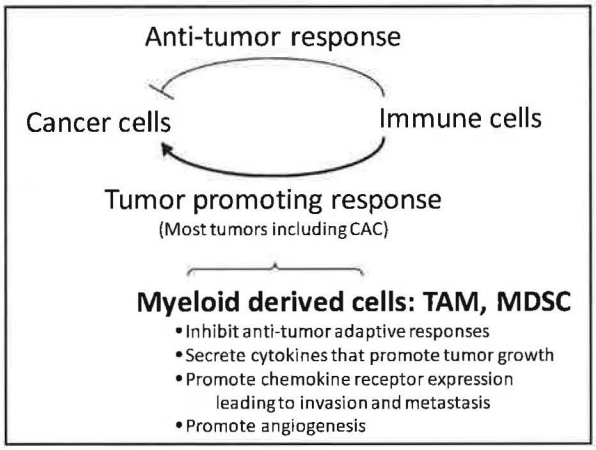
and liver fluke infection, pancreatic cancer which is associated with chronic pancreatitis, and hepatocellular carcinoma, whose risk is increased in patients with chronic hepatitis and cirrhosis. Moreover, malignancies outside of the GI tract offer additional examples such as squamous cell carcinoma of the bladder in patients with schistosomiasis. Finally, it is broadly recognized now that evidence of smoldering inflammation in the form of an inflammatory infiltrate and cytokine production is nearly universally seen in solid tumors. The term tumor-related inflammation has been coined to refer to this immune response. Therefore, the relationship between inflammation and cancer is a broader paradigm, and the study of the pathophysiology of CAC has provided important clues into how these processes are related.

Cancer as a complex tissue that includes immune cells

In a landmark review of cancer pathogenesis in 2000, Hanahan and Weinberg described six characteristics of the cancer cell, which are broadly shared by multiple tumor types, irrespective of the diversity of genetic pathways that are involved in carcinogenesis in different tissues. This concept has come to dominate the field of cancer research. In addition, they noted that *"the field of cancer research has largely been guided by a reductionist focus on cancer cells and the genes within them..... looking forward in time, we believe that new inroads will come from regarding tumors as complex tissues".* This meant to convey the notion that non-neoplastic cells within the tumor likely play critical roles in tumor growth, maintenance and spread. In fact, today there is extensive evidence that indeed stomal/mesenchymal cells, endothelial cells and immune cells all play critical roles in tumorigenesis. In this regard, CAC has provided an important clinical and experimental paradigm to examine the role of the immune system in cancer development.

Tumor promoting immune responses

Already in the 19th century, the famed pathologist Virchow suggested that inflammation played a critical role in cancer development. Nevertheless, our view of the inflammatory response to cancer has been dominated by the notion that immune responses are generally anti-tumor. Evidence of this type of immune response can be seen in certain tumors, such as sporadic colon cancer, where lymphocytic infiltration, particularly by Th1-CD4+ cells is associated with better outcomes. In addition, immune surveillance is critically important to avert cancer formation, as demonstrated by the increased risk of cancer in patients with immunodeficiency. Moreover, anticancer effects of graft-vs-tumor responses are known to be important in the ultimate outcome of allogeneic bone marrow transplantation in the treatment of various hematologic malignancies. Having said all this, evidence that immune cells commonly play a tumor supporting role has mounted over the past decade.



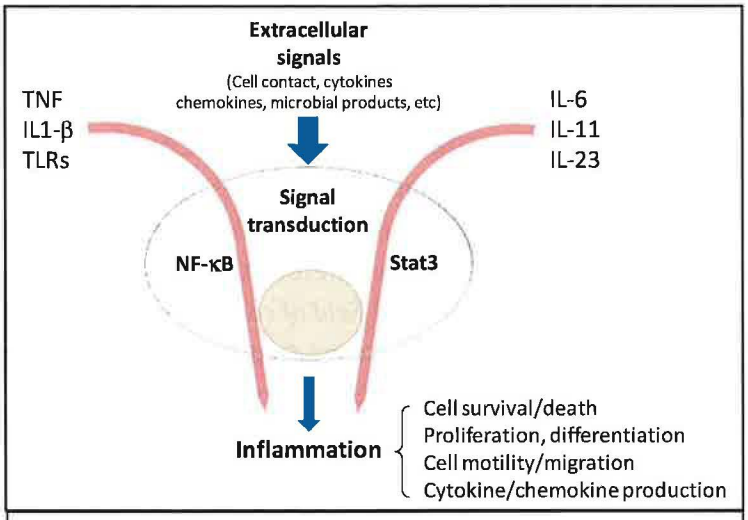
Cells of myeloid origin that promote tumor development have been described and characterized in a variety of ways including adoptive transfer experiments. These cells are in some cases referred to as tumor-associated macrophages (TAM) or myeloid derived suppressor cells (MDSC). In general, these cells have been shown to inhibit anti-tumor adaptive responses. They secrete a variety of cytokines that have trophic effects on cancer cells, promoting tumor growth. Moreover, through these soluble factors, TAMs promote chemokine receptor expression in cancer cells, a step leading to invasion and metastasis. Finally, these cells have been also found to be partly responsible for promoting tumor angiogenesis. In addition to myeloid cells with tumor promoting activities, T regulatory cells that dampen Th1-directed anti-tumor activities and help polarize myeloid cells towards a tumor supporting phenotype have been reported in a variety of malignancies.

Cytokines and chemokines as growth factors for cancer cells

A variety of tissue insults, including microbial infiltration, are ultimately sensed by specialized cellular receptors, setting in motion the inflammatory cascade through a set of inter-cellular signals in the form of cytokines, chemokines, and

direct signaling through cell-cell contact. These various signals are ultimately translated by intracellular signal transduction mechanisms in resident-tissue cells and immune cells leading to a variety of physiologic changes in cell behavior, including proliferation, differentiation, cell survival or death, cell motility, migration, and the production of additional mediators of inflammation such as cytokines and chemokines, that amplify or modulate the response.

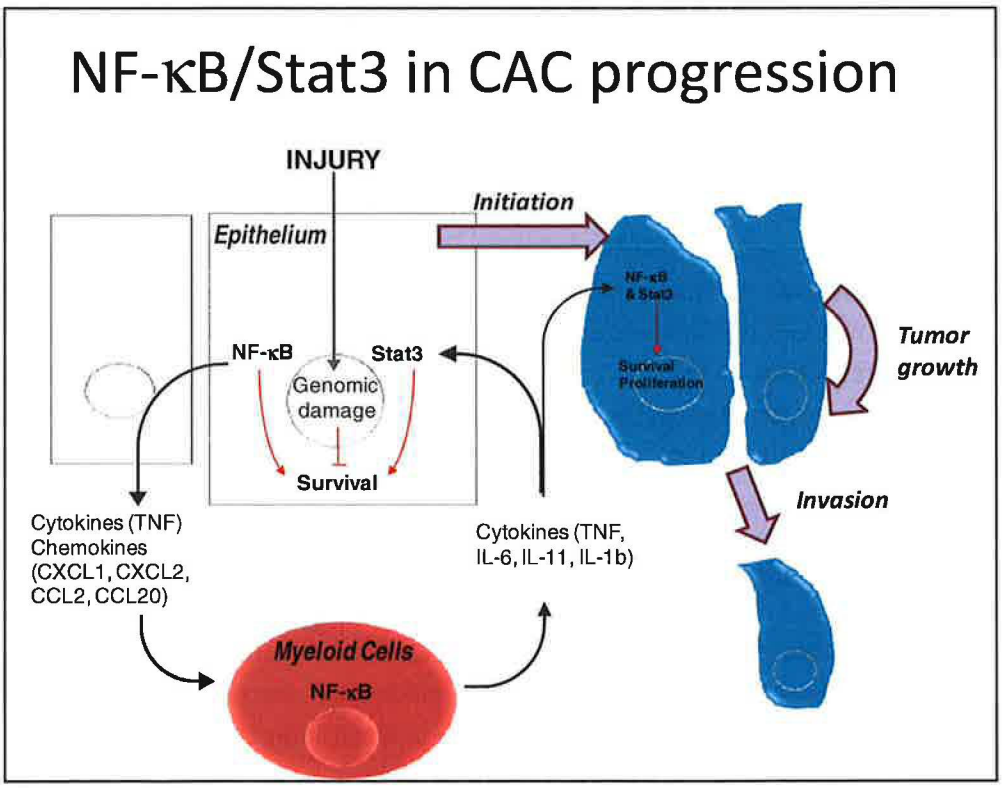
These alterations of cell behavior affect not only immune cells, but also non-immune cells within the tissue, and can be co-opted to the benefit of the cancer cells. As such it has been appreciated that various cytokines can promote cancer cell survival, proliferation, migration and invasion. Acting through autocrine loops, oncogene activation is frequently accompanied by pro-inflammatory gene expression, which is subsequently amplified by a tumor promoting immune response which serves to 'feed' tumor growth. In the case of CAC, animal models have demonstrated a tumor promoting role for several cytokines including TNF, IL-1β, IL-6, IL-11, IL-23 and TLR activation. In addition, two intracellular signal transduction cascades have been recognized as playing critical roles in CAC development, namely the NF-κB and Stat3 pathways.



Cytokines with tumor-promoting activities in CAC

NF-κB in CAC development

NF-κB is a dimeric transcription factor ordinarily sequestered in the cytosol under basal conditions through its interaction with the inhibitor of κB (IκB). Activation of this pathway requires IκB degradation, a step triggered by IκB phosphorylation by the IκB kinase or IKK complex. This leads to nuclear accumulation of NF-κB and gene induction, ultimately resulting in increased expression of pro-inflammatory and pro-survival factors. Termination of NF-κB is mediated by IκB resynthesis and NF-κB export from the nucleus, as well as degradation of nuclear, DNA-bound NF-κB through a pathway that requires the co-factor COMMD1. In addition, IKK activation is subsequently down-regulated by proteins such as A20 and Cyld.



It has been long recognized that NF-κB activation is frequently observed in most tumors. With the exception of a few hematologic malignancies, most cancers do not bear mutations in the NF-κB pathway itself, and tonic activation is thought to result from the pro-inflammatory environment around the tumor. Acting through its

effects on cell survival, this activation of NF-κB is thought to be beneficial to tumor growth and may play a role in cancer chemo and radioresistance. Moreover, given the ability of NF-κB to drive expression of a large number of pro-inflammatory cytokines, chemokines and other mediators, its activation serves to greatly amplify inflammatory responses.

The role of NF-κB activation in CAC has been studied in mice with the use of tissue specific inactivation of IKKβ, a critical catalytic subunit of the IKK complex, which results in poor NF-κB activation. Using repeated applications of dextran sodium sulfate to induce chronic colitis and administration of small doses of the carcinogen azoxymethane, mice go on to develop chronic colitis and cancer, which recapitulates many aspects of CAC. Using this model, it was found that epithelial NF-κB activation is required early in the neoplastic process for tumor cell survival. Impaired NF-κB activation in the IKKβ intestinal epithelial knockout led to increased apoptosis of the epithelium during colitis and decreased number of subsequent tumors. On the other hand, NF-κB activation in myeloid cells was found to be necessary for the supportive role of this cell population in tumor growth. Myeloid-specific IKKβ deletion led to decreased NF-κB activation in these cells, which was accompanied by reduced cytokine production in the inflamed mucosa, and smaller and fewer tumors arising in these mice. Other alterations in NF-κB regulation also modulate CAC development in this model. Cyld deficiency, which leads to exaggerated NF-κB activation, led to more severe and rapid progression to CAC in mice. Similarly, COMMD1 deficiency which also leads to increased NF-κB activation is frequently observed in invasive and aggressive tumors promoting cancer invasion in a variety of settings. Finally, acting in a paracrine fashion, IL-6 and IL-11 production by myeloid cells, promote tumor growth through activation of Stat3, a key transcription factor.

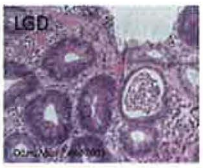
Managing our patients: Surveillance

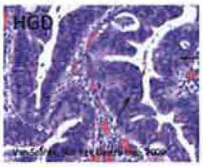
The objective of surveillance is to identify early cancers, at a stage where curative intervention can be offered, or the precancerous lesion, in this case dysplasia. While all professional societies endorse the use of colonoscopy for surveillance in this patient population, there are no randomized-controlled trials demonstrating the efficacy of this approach. The only evidence available is from population-based and case-control studies that demonstrate that patients in surveillance programs are diagnosed at earlier stages than patients not enrolled in surveillance. However, whether this truly impacts long-term outcomes, or simply constitutes lead-time bias, is an unresolved

Riddell classification

(Riddell et al, Hum Pathol, 1983):

- Negative
- Indefinite
- LGD
- HGD





Surveillance: When to start?

- ASGE guidelines (Davila et al, GI Endoscopy, 2006):
  - Extensive dz (1/3 of the colon histologically): 8-10 yrs of Dx, repeat every 1-2 yrs
- AGA guidelines (Farraye et al, Gastroenterology, 2010):
  - All patients should have an exam at 8 yrs to stage disease extent microscopically
  - Extensive disease (more than proctosigmoiditis, 1/3 colon involvement in CD), should start 1-2 yrs later, repeat every 1-3 yrs if no dysplasia
  - PSC patients: immediately upon diagnosis

Surveillance: How to do it?

- ASGE: Four biopsies every 10 cm, a minimum of 33 samples (based on Rubin et al, Gastroenterology, 1992)
- AGA: Representative biopsies from each anatomical section of the colon; a minimum of 33 biopsies also accepted.

controversy. Nevertheless, given the magnitude of risk, performing prospective randomized trials on the efficacy of colonoscopy is not considered ethical and such trial are unlike to ever be done.

Surveillance: When to start and How to do it

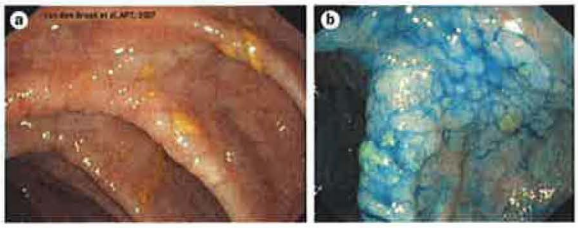
The most recent recommendations by the American Society for Gastrointestinal Endoscopy advice that surveillance should be offered to patients with extensive disease, involving at least 1/3 of the colon histologically. Surveillance should be initiated after 8-10 yrs of disease, and should be repeated at 1-2 yr intervals. The American Gastroenterological Association issued its most recent recommendation on CAC surveillance this past year. The AGA panel recommended that all patients with IBD should have an exam at 8 yrs to stage the extent of disease microscopically. This is based in part on the known propensity of patient with limited disease to develop more extensive inflammation over time. Based on this examination, patients with extensive disease, involving more than 1/3 of the colon in CD or more than proctosigmoiditis in UC, should start surveillance exams 1-2 yrs later. The recommended interval for subsequent repeat exams was 1-3 yrs in the absence of dysplasia, to be individualized based on additional risk factors in each patient. In addition, given the high risk for CAC in PSC patients, it was recommended that these patients be enrolled in yearly surveillance immediately upon diagnosis and without waiting 8 years as in other IBD patients. At the present time, both American societies still endorse the use of random colonoscopic biopsies as the main approach to surveillance, with a minimum of 33 specimens being recommended. Suspicious lesions should be directly biopsied as well. The ASGE specified that 4 quadrant biopsies every 10 cm is a preferred approach to random biopsies, which is commonly practiced. Nevertheless, advances in imaging technologies are challenging the role of random biopsies as the mainstay of CAC surveillance (see below).

Dysplasia and concurrent cancer

As stated previously, patients with dysplasia and cancer frequently display molecular evidence of extensive mutagenic injury throughout their colon, and the histologic changes can be multifocal. In addition, it has been traditionally regarded that dysplasia and even cancer can be endoscopically invisible. This concern was borne out from an analysis of prior studies, published by Bernstein in the Lancet in 1994. This analysis indicated that in an alarming number of patients, cancers were found at the time of colectomy that had not been noted by the endoscopist. In specific term, 42% of patients with HGD in random biopsies had concurrent cancer, and 43% or patients with an unresectable mass or lesion that demonstrated dysplasia in endoscopic biopsies were found to actually have cancer in the surgical specimen. Moreover, the same study found that LGD was also associated with a high risk of concurrent cancer found only after colectomy (19%), and the risk of subsequent development of HGD, DALM or CAC was similarly high (29%).

	Risk of cancer or advanced neoplasia			
Study	DALM	HGD	LGD	No dysplasia
Bernstein, Lancet, 1994 Analysis of 10 prospective studies, n=1225	43%	42%	19% (Concurrent Cancer) 29% (DALM,HGD, Ca on f/u)	2% (on f/u)
	Concurrent Cancer NOT SEEN!			
Lindberg, Scand J Gastro, 1996 Analysis of 20 yr experience at one center, n=143			41% (HGD or Ca on f/u)	
Ullman, Gastro, 2003 Analysis of outcomes in flat LGD at Mount Sinai, n=45			30% (HGC or Ca on f/u)	
Lim, Gut, 2003 Outcomes of LGD in a single center in the UK, n=29			10% (HGD or Ca at 10 y f/u)	

Chromoendoscopy is a better imaging modality



- Metanalysis of 6 studies with 1277 pts (Subramanian et al, APT, 2010)
- 12% rate of dysplasia or 1/8 patients
- Detects 7% more pts with dysplasia
- Detects 44% more dysplastic lesions in targeted biopsies
- Takes 11 min longer

The observations regarding the risk of CAC or HGD in patients with LGD have been recapitulated by some but not all subsequent studies. Moreover, it has been repeatedly noted that there is poor interobserver agreement among expert pathologists with regard to the diagnosis of LGD, suggesting that this is less homogeneous and reliable pathologic diagnosis.

Despite the alarming rates of unrecognized cancers noted by Bernstein, more recent studies suggest that most dysplasia and cancer are actually visible with modern endoscopic instrumentation and techniques. Endoscopy has actually undergone substantial advances in the past 10 years. In particular, image resolution has improved considerably, and now includes high definition display, which greatly enhances image quality. In addition, the use of dye spraying to accentuate mucosal detail, a technique known as chromoendoscopy, almost doubles the visualization of abnormal lesions over conventional white light endoscopy at the cost of 11 additional minutes during the procedure. For all these reasons, most specialized IBD centers have adopted chromoendoscopy as the preferred modality of examination, and several experts now report doing only targeted biopsies based on their visualization with this technique. At this point in time, the recommendations by the AGA endorse chromoendoscopy as a viable alternative, but do not present this approach as the mainstay of surveillance. However, the British Society of Gastroenterology already recommends chromoendoscopy as the preferred technique for surveillance, and it is likely to become the norm in the USA over time.

Limitations of surveillance

Patients with extensive pseudopolyps pose a clear problem for endoscopic surveillance. On the one hand, this group is known to have a higher risk for CAC, and on the other, the mucosal alterations make it nearly impossible to identify early raised lesions that should be biopsied or removed. For these reasons, it is very hard or impossible to provide adequate surveillance in these patients and many experts recommend colectomy in this patient population. Close yearly surveillance is probably warranted in those patients not amenable or willing to have surgery.

Another important limitation is the distortion produced by active inflammation. This not only presents a problem for the identification of suspicious lesions for the endoscopist, but can induce regenerative changes histologically that can result in indefinite or LGD readings. For these reasons, whenever possible, surveillance exams should not be done during an active inflammatory flare of the disease.

What to do if you find dysplasia

This is an evolving topic, and current recommendations reflect the recent advances in visualization of lesions that are now possible with current instruments and techniques. Three main scenarios arise, which are described below:

1) Raised discrete, endoscopically-resectable lesions: If such lesions are encountered, the current recommendation is to completely remove the lesion if this is endoscopically possible, and to biopsy the surrounding mucosa to ensure complete resection. If upon pathologic examination, dysplasia is found in this lesion, the patient can be observed with close surveillance if complete resection was achieved and no other areas of dysplasia were found. This recommendation is made regardless of the degree of dysplasia, including HGD, so long as complete resection is assured and no concomitant dysplasia is noted elsewhere.

2) Lesions that are not resectable endoscopically: This group encompasses a variety of scenarios including a large mass (DALM) that was biosied, an area of flat mucosal abnormality that is visible but too extensive to be resectable, lesions that are multifocal in nature and thus not amenable to resection, or abnormalities that are not visible endoscopically but are known to be there based on random biopsies. In the event that the histological diagnosis is HGD, the recommendation is colectomy given the concern for progression of HGD to invasive cancer or for a synchronous undetected cancer. In the event of LGD, there are two schools of thought. Those that are concerned about the low reliability of the pathologic diagnosis recommend to have the biopsies re-read by an expert GI pathologist and/or to repeat the exam in 6 months to obtain additional biopsies. On the other hands, other authorities concerned more with

the high rates of synchronous or metachronous malignancy in LGD, recommend surgery for this patient population as well.

3) Patient with a diagnosis of indefinite for dysplasia: These patients should have a repeat exam at a shorter interval of 3-12 months to further define whether dysplasia is indeed present.

Chemoprevention

A number of factors that seem to provide protection against the development of CAC have been reported. Among them are the use of Mesalamine, the use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) and the use of ursodiol. Mesalamine products have been extensively studied in this regard and many studies have found them to reduce the risk of cancer in UC patients. Nevertheless, the evidence is not uniform and plenty of negative studies have been reported. Altogether, the recent AGA panel graded the evidence for a chemopreventive effect of mesalamine as likely (grade B evidence) and these drugs are the most commonly with this indication in mind. Ursodiol, which has been studied in patients with PSC, has been reported by two groups to provide protection from colon cancer and dysplasia in this patient population. The chemopreventive effect of Ursodiol stands in contrast with the fact that this drug does not alter the natural history of the biliary disease in the patients.

Studies of other disease-controlling agents, such as corticosteroids or azathioprine, have not demonstrated a chemopreventive effect. Anti-TNF agents decrease CAC in animal models, but human data is at this point lacking. Aspirin and NSAIDs have been previously reported to have a chemopreventive effect of in sporadic colon cancer and in patients with polyposis syndromes. Population studies in IBD patients also made a similar observation with regards to CAC. Nevertheless, use of these drugs in this patient population has not been recommended, probably because NSAIDs have been reported to produce an enteropathy that mimics IBD and may in fact exacerbate IBD symptoms as well.

Conclusions

- IBD patients with extensive, prolonged involvement have an increased risk for cancer
- CAC follows a colitis/dysplasia/cancer sequence that resembles but is unique from sporadic cancer
- The immune system plays a promoting role in cancer progression
- Surveillance after 8-10 yrs of disease is recommended
- Endoscopic and surgical options may be required to address advanced neoplasia in these patients

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