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Colon Cancer: Inflammation Associated Cancer

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SYNOPSIS

Colitis-associated cancer (CAC) is a relatively rare form of cancer with an unclear pathogenesis. CAC serves as a prototype of inflammation associated cancers. Advanced colonoscopic techniques are considered standard of care for surveillance in patients with long-standing colitis, especially those with other risk factors including sclerosing cholangitis and family history of colorectal cancer. When CAC is diagnosed, the standard operation involves total proctocolectomy. Restorative procedures and surveillance post colectomy require special considerations. In these contexts, new 3D human models may be utilized to usher in personalized medicine.

Keywords

Colitis-associated cancer; colitis cancer surveillance; colitis-associated cancer management; 3D human models

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I. Introduction

While colitis-associated cancer constitutes less than two percent of all colon cancers[1], the challenges associated with this type of this cancer have implications that relate to many other cancers including disease progression, lack of clarity regarding pathogenesis, and broader context for all inflammation-associated cancers.

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is associated with an increased risk for developing colorectal cancer (CRC). Historically, some advocated prophylactic colectomy for patients with longstanding UC in order to reduce CRC related mortality.[2] While the exact magnitude remains unknown, patients with IBD are known to have an increased risk of developing colorectal neoplasia. This discrepancy in incidence is due to the wide variability in reported results as a result of variations in sources of information, such as data from low volume vs high volume centers, population-based data vs case reporting, and other small series.[3] In a large meta-analysis of 116 studies, the risk of cancer in patients with mucosal ulcerative colitis (UC) after disease duration of 10, 20, and 30 years was estimated to be 2%, 8% and 18% respectively. The reported prevalence of CRC in this analysis was 3.7%[1]. Another report of a 30-year surveillance program calculated the risk of neoplasia (both dysplasia and carcinoma) to be 7.7% at 20 years. This risk reached 15.8% at 30 years of disease duration.[3] In another analysis of a 30-year colonoscopic surveillance program in patients with UC, the cumulative incidence of CRC was 2.5%, 7.6%, and 10.8% at 20, 30, and 40 years of disease, respectively[4]. Comparable findings have been demonstrated in CD and the reported incidence was 8% at 22 years.[5] Similarly, the cumulative risk of CRC in CD was reported as 0.3%, 1.6%, and 2.4% at 5, 15, and 25 years after diagnosis.[6]

CRC is one of the most devastating complications of IBD. It is associated with significant morbidity and mortality up to 15%[7,8]. To reduce the risk of CRC in these patients, endoscopic surveillance guidelines have been developed to allow detection and potential removal of precancerous lesions. Such strategies aim to decrease CRC incidence in patients with IBD and improve mortality rates[7,9].

With the availability of colonoscopy to evaluate the extent of the disease related to IBD and obtaining tissue biopsies, and realizing the risk factors associated with developing CRC in IBD patients, efforts have been made to limit and/or prevent CRC-related mortality, while maximizing organ preservation. The increased risk for IBD-associated CRC prompted the practice of surveillance colonoscopy in these patients[10]. Despite lack of prospective controlled trials to evaluate f risk, benefit, and cost effectiveness of this surveillance approach, sufficient evidence is available to support the broad adoption of these strategies. Subsequent reports showed less risk of CRC which could be attributed to either more timely surgical intervention, or perhaps more usage of chemopreventive agents such as aminosalicylates, or possibly more implementation of surveillance colonoscopy [3,7,10].

II. Epidemiology

Risk Factors for Developing Carcinoma in IBD Patients

There are some factors that had been associated with increased risk of developing colorectal cancer (CRC) in patients with IBD.

Age at onset of disease—Early age at onset of IBD disease has not been consistently shown to represent an independent risk factor for CRC. However, it reflects longer duration of disease with associated colitis-related burden of increased risk of malignancy. The cumulative risk of CRC in patients with extensive UC has been estimated to be 40% in patients who had the disease before 15 years of age and 25% in patients who developed the disease between 15 and 39 years of age.[11,12]

Duration of disease—The relationship between disease duration and risk of neoplasia is proportional. It has been demonstrated that the longer the duration of the disease the higher risk of developing CRC that is significant after 8 years of disease. While CRC can arise before 8 years, this happens in small proportions of patients and is sufficiently infrequent to justify commencing surveillance earlier than 8 years [13].

Anatomic Extent of disease—The risk of CRC has been attributed to the extent of disease in both UC and CD. Based on the anatomic extent in UC, patients are classified into 3 categories; Extensive, with inflammation proximal to the splenic flexure; Left-sided, in which presence of disease is located in the descending colon up to (but not proximal to) the splenic flexure, and proctosigmoiditis, where disease is limited to the rectum with or without sigmoid colon involvement[12]. In UC, the risk for CRC is highest in patients with extensive disease, and intermediate in those with left-sided disease, while patients with proctosigmoiditis are at no or minimal risk of CRC.[3]

Histological changes versus macroscopic changes—A proportional relationship exists between degree of histologic inflammation and risk of CRC. Indeed, CRC can arise in endoscopically normal mucosa that shows histologic evidence of disease on pathology. Additionally, carcinoma may also arise in regions where active colitis has remitted, i.e., areas with no active inflammation but with histologic findings of inactive colitis in areas where the mucosa had never been inflamed, the risk of neoplasia is not increased and remains comparable to the non-IBD population[3].

Therefore histologic abnormalities are a more reliable determinant of disease status and risk for carcinoma than are macroscopic changes. Thus, the anatomic extent of the disease should be determined based on both endoscopic and histologic evaluation, whichever reveals more substantial evidence of involvement which could be done either at time of diagnosis or screening. For surveillance purposes, microscopic evaluation should be included in the assessment rather than endoscopic images alone. For example, a patient with macroscopic evidence of disease only in recto-sigmoid junction, but has histologic evidence of active inflammation in the descending colon should undergo surveillance according to left-sided extent of the disease. Furthermore, patients with CD who have more than one third of their colon involved are at increased risk for CRC.

Back wash ileitis and risk of CRC—Inflammation in the ileum associated with colitis in the ascending colon and cecum is known as back-wash ileitis. There is no evidence to suggest back wash ileitis as an independent risk factor for developing CRC [3,12].

Primary Sclerosing Cholangitis (PSC)—There is a strong association between PSC and CRC in IBD patients. In a recent meta-analysis the risk of CRC in UC patients with PSC increased 4-fold when compared to UC patients without PSC. This intrinsic risk remained after liver transplant at a rate of 1% per patient per year. Patients with PSC may harbor a subclinical form of colitis (either UC or CD) for an extended duration prior to their diagnosis. Therefore, patients with PSC and IBD are recommended to commence annual colonoscopy from the time of diagnosis of PSC. In addition, they are recommended to continue surveillance after liver transplant [3,10,12,13].

Family History of CRC—Positive family history is regarded as an important independent risk factor with regard to CRC development. An IBD patient with a positive family history for a sporadic CRC in a first degree relative has double the risk of developing CRC. Furthermore, if that first degree relative was younger than 50 years of age at time of diagnosis, this risk will increase to 9-fold in the IBD patient. While family history is regarded as independent risk factor for developing CRC in IBD patients, it is unclear if this should independently influence the surveillance intervals[3,12,13].

Other factors/Special considerations—Colorectal strictures, especially in UC, are associated with increased risk of developing neoplasia[14]. Similarly, the presence of a foreshortened colon; as indicative of long-standing inflammation, raises the concern for developing malignancy. The presence of these features requires extra vigilance by the endoscopist during screening/surveillance and warrants extra biopsies with potentially shorter intervals between surveillance colonoscopies.

II. Pathogenesis

The pathogenesis of ulcerative colitis is unclear and subsequently the progression of colitis to inflammation to cancer is similarly unclear. Some combination of genetic susceptibility, exposure to antigens in the microenvironment, and immune reactivity governs the range of clinical phenotypes [15]. However, the relationship between these elements is not clear and therefore, prevention and therapy are challenging.

First, the genetics are complex. While there have been multiple genes that have been associated with inflammatory bowel disease and less specifically with ulcerative colitis, the precise correlations are less robust than they are for sporadic colon cancer. Indeed, the adenoma to carcinoma sequence[16])is not so reliably reproduced. In fact, a variation of this sequence, known as the inflammation to dysplasia to carcinoma sequence is believed to be operative. In this sequence, noted genetic mutations in p53, Kras, and APC, occur in a sequence and with frequencies far different than in sporadic colon cancer. For example, the initiating mutation in colitis is believed to be in p53, where there may be a field effect in long-term clinically quiescent or minimal disease[16–18]. For example, sporadic CRCs are associated with *APC* mutations early in their pathogenesis. In contrast, CAC is believed to

acquire p53 mutations or loss of heterozygosity early in its pathogenesis, with *APC* aberrations occurring later. In CAC, allelic deletion of p53 occurs in ~50% of cases.[19] More recent studies using next generation sequencing indicate that genetic alterations occur in upwards of 89% of patients[20,21]. Indeed, such mutations were identified in non-dysplastic, but chronically inflamed mucosa[22]. Overall, genome-wide mRNA and miRNA profiles are quite different comparing sporadic CRC vs. CAC[23].

While genetics and epigenetic influences undoubtedly contribute to the propensity of the phenotype, the microenvironment and how the gut reacts to these challenges controls the phenotype. The microenvironment in this context has two major components: the cellular microenvironment and the microbiome (Figure 1). As ulcerative colitis and downstream dysplasia result from these interactions, they must be considered in the pathogenesis, and potentially as therapeutic targets. The cellular elements of the microenvironment include multiple cells types including neutrophils, monocytes, T cells, fibroblasts, and the endothelia. As this process is driven by inflammation, the inflammatory secretome of these cells, as well as their functions in antigen-presentation, wound healing, management of injured and dead cells, as well as the interactions with gut bacteria and environmental exposures are the key to reconciling the inflammatory process in a positive or a pathological manner. In this process, the microenvironmental influences especially including the influences of known inflammatory cells, such as neutrophils, monocytes, and T cells, with their secreted chemokines/cytokines, by the inflammatory and proliferative cascades that are initiated[18,24]. Dominant signaling pathways involved are WNT, STAT3, TNFα and NFKβ[25–28]. The second aspect of the microenvironment, but constituting an increasingly more important contribution to this environment, are the bacteria. The load of bacteria in the colon is estimated to be 10^{11}per gram of tissue[17]. These bacteria have been noted to supply nutrients for the colon, provide a protective barrier from pathogens in the colon, and aid in the development of the gut immune system. The relationship between these bacteria and the host epithelia and microenvironment requires a symbiotic balance to remain in check.

Within the epithelia themselves, the mucus secreted by goblet cells is a barrier against infiltration by bacteria and pathogens. This sticky gel-like coating helps to maintain gut homeostasis. During attacks of colitis, the integrity of this coating is violated, thus permitting contact of the pathogens with the underlying immune system that lies deep to the stroma. Other epithelial cells, including Paneth cells, constitute gut defenses. Here the secretion of antimicrobial peptides such as defensins and lysozyme also protective. Notably, Paneth cells are not usually present in the colon. However, following an acute attack, these cells, which constitute the regenerative niche of the colonic crypts, reappear, seemingly to prepare a bed for new colonic crypts to repopulate the mucosa[29].

III. Surveillance

In the era of preemptive and preventive practice of medicine, at-risk IBD patients should undergo surveillance colonoscopies at regular intervals, depending on level of risk. While the efficacy of endoscopic surveillance has not been evaluated in prospective randomized controlled trials, evidence based on case series, case control studies, and population-based cohort studies had demonstrated some benefits suggesting earlier detection of cancer and

possibly improved CRC-related survival[13]. The more long-standing duration and extensive expression of UC or Crohn's colitis puts the IBD patient at higher risk for developing dysplasia and CRC [10]. Further, as previously mentioned, the extent of the disease does not necessarily correspond to the visually inflamed mucosa examined endoscopically, as colonoscopic imaging can underestimate the extent of disease.

In a Cochrane analysis[30] there was no clear evidence that surveillance colonoscopy prolongs survival, whereas, a subsequent cohort study reported a 100% CRC-related 5-year survival in 23 patient who received surveillance compared to 74% in non-surveillance group[31]. One analysis demonstrated that surveillance colonoscopy could be cost effective when performed in high risk group of patients who has extensive colitis with moderate or severe active inflammation, PSC, family history of CRC in first degree family member aged <50 years at diagnosis, any degree of dysplasia encountered in previous 5 years.

According to the American Gastroenterology Association guidelines published in 2010, the recommendations were to obtain 4 quadrant biopsies every 10 cm summing for at least 33 "random" tissue specimens from all segments of the colon and rectum in an attempt to detect endoscopically invisible flat lesions as well as biopsy or resect all visible lesions.[3]

Visible vs. Invisible Lesions and White-light endoscopy vs. Chromoendoscopy

The practice of random biopsies arose in early 1980's in the era of fiberoptic and early video endoscopy where dysplasia was surprisingly found in a biopsy taken from unsuspected mucosa. Hence, the term "invisible dysplasia"[32]. Subsequently, it was observed that patients who had biopsies from a lesion or a mass were found to have colorectal neoplasia, thus, the term "dysplasia-associated lesion or mass" was coined[32,33]. Random surveillance biopsies effectively samples about 1% of colonic mucosa[34,35]. Furthermore, it has been estimated that in order to detect one colorectal neoplasia, 1266 random biopsies were needed[36].

Image-enhanced endoscopy in IBD surveillance using high-definition chromoendoscopy enabled endoscopists to identify the previously deemed invisible dysplasia detected on random biopsy, and made them visible in majority of patients.[13] Surface chromoendoscopy enhances areas of mucosal nodularity and highlights regions with topographic abnormalities, such as depressions and elevations which could be missed on standard white-light endoscopy. Randomized and case control studies have shown a two- to three-fold improvement in per-patient dysplasia detection and four to five folds increase in per-lesion dysplasia detection when chromoendoscopy was used[37–41]. A meta-analysis of prospective studies comparing chromoendoscopy to standard definition white-light endoscopy showed that chromoendoscopy with targeted biopsies is associated with 7% increase in detection yield, and the calculated the needed number to treat in order to detect one additional patient with neoplasia (dysplasia or cancer) is 14.3 (95% CI 9.7 – 30.3)[42]. Once the lesion is identified, chromoendoscopy will enable to delineate the lesion morphology, size, and border, in addition to evaluating for any endoscopic features of submucosal invasion.[13]

If deemed resectable, then the lesion should be tattooed and resected or referred to an endoscopist with expertise in endoscopic mucosal resection and/or endoscopic submucosal dissection. Additionally targeted biopsies should be obtained from lesions thought to be

unresectable as well as lesions of uncertain significance[13]. The mucosa surrounding lesions that underwent endoscopic resection should also be biopsied to ensure that margins are free from dysplasia. The benefit of surveillance may be compromised in the context of pseudopolyps. As affected patients should be made aware of this fact, some will opt for prophylactic colectomy over continuing surveillance in this situation.[3]

Dysplasia in IBD

In patients with IBD, dysplasia is defined histologically as an unequivocal neoplastic changes of the intestinal mucosa in the background of chronic inflammation. It can also be classified as an endoscopically visible dysplastic lesion that is detected via resection or targeted biopsy, or an endoscopically invisible lesion detected by random biopsies[13]. While dysplasia is a good marker of developing CRC cancer, there are limitations in predicting the natural history of dysplasia in IBD patients. Dysplasia is present in 75% to 90% of patients with IBD-related cancer, although, carcinoma may occur without a prior history of dysplasia.[3,12] Taylor et al. found 26% of cancer in proctocolectomy specimens without any coexisting findings of dysplasia.[43] Furthermore, patients with low-grade dysplasia (LGD) do not necessarily evolve into an antecedent phase of detectable high-grade dysplasia (HGD) prior to developing CRC. [3,12]

Type of Lesions detected endoscopically

The Paris classification[44] is a simplified method to describe endoscopically visible lesions, and has led to abandoning using the term “DALM (dysplastic associated lesion or mass)”[44–46]. In this classification lesions are categorized into polypoid (where lesions are protruding >/= 2.5 mm from mucosa into the lumen) and non-polypoid (lesions with no or little protrusion< 2.5mm above the mucosa). Polypoid lesions can be described as pedunculated or sessile. Non-polypoid lesions are further classified as slightly elevated, flat, or depressed. The location of the lesion should be identified as within or outside an area of known colitis. In addition, lesions borders should be described as distinct or indistinct. Furthermore, special attention should be given to evaluate for presence of overlying ulceration or any other signs indicative of submucosal invasion including depressions and/or failure of mucosal lift upon attempting submucosal injection.[47,48]

Histologic Interpretation

Pathological evaluation of surveillance biopsy specimens in IBD patients, should be undertaken in accordance to the recommendations of the “IBD Dysplasia Morphology Working Group” findings published in 1983.[12] Importantly, the pathological interpretation of dysplasia had been notorious for inter-observer variability in mucosal biopsy specimens. Thus, pathologists with expertise in gastrointestinal disorder should be able to review and confirm findings[3]. Active inflammatory changes may impose some challenges on pathologic evaluation of biopsy specimens for dysplasia. However, the disease activity per se does not preclude accurate pathological interpretation. Accordingly, endoscopic examination should not be deferred for lengthy time intervals in patients with active inflammation merely for the purpose of increasing diagnostic accuracy. Nonetheless, postponement for acceptable time interval for any intervention to reduce inflammation is reasonable[12].

Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory bowel disease Patients

International Consensus Recommendations: (SCENIC) [48]—Despite the overall agreement on CRC neoplasia in patients with IBD, there had been lack in consistency regarding surveillance, techniques, nomenclature, management and follow-up. Therefore, unifying consensus recommendations on the surveillance and management of dysplasia in IBD patients were needed. The SCENIC international consensus aimed to address methods for detection and management of colitic dysplasia. The consensus working group developed recommendations regarding description of dysplasia and ultimately, recommendations were made on how to implement the recommendations in clinical practice.[49].

Classification (Nomenclature) of IBD Dysplasia—The term DALM can be polypoid, non-polypoid, or a mass-like lesion, therefore, it is not specific and may cause confusion. In order to avoid confusion, a subgroup of panelists devised new set of terms based on the descriptive terms used in Paris classification[44] to describe the macroscopic appearance of dysplasia in IBD (see above). Therefore, The SCENIC panelists recommended abandoning the term “DALM”[48]. The term “endoscopically resectable” should be used when, and indicates: (i) clearly identified and distinct margin of the lesions; (ii) resectability seems feasible on endoscopic evaluation and appears completely removed upon evaluation post-resection; (iii) histopathologic examination confirms complete resection as well as absence of dysplasia in biopsy specimens obtained from mucosa immediately adjacent to the resection site.[48]

Further, SCENIC recommended use of chromoendoscopy when performing surveillance colonoscopy in patients with IBD rather than white-light endoscopy. Thus, shifting the clinical practice from random towards targeted biopsy technique. The statistics of studies comparing chromoendoscopy with white-light standard definition colonoscopy alone showed a significant increase in rate of identifying patients with dysplasia using chromoendoscopy (relative risk = 1.8 [1.2–2.6])[32,48]. When surveillance is undertaken using white-light endoscopy, high definition is recommended rather than standard definition. Image-enhanced narrow-band imaging is not suggested in place of white-light colonoscopy or chromoendoscopy.[48]

IV. Management of CAC

Management of Endoscopically Visible Lesions

Lesions identified in a known segment of inflamed colon during surveillance colonoscopy and deemed resectable should undergo endoscopic resection aiming to achieve complete resection. Biopsies from the flat mucosa adjacent to the resection site should be obtained to ensure lateral margins are free of dysplasia[13,47]. The most important principle is to maximize the potential for complete eradication on first attempt. En bloc resection allows evaluating completeness of resection as well as margin status which is crucial for subsequent decision making.[7]

Provided that there is no endoscopically invisible/flat dysplasia, a complete resection confirmed on histopathological evaluation prompts close monitoring and surveillance. According to the SCENIC recommendations, after histologic confirmation of complete resection for polypoid and non-polypoid lesions, the SCENIC statement "suggested" surveillance colonoscopy for such lesions rather than colectomy after "complete" removal with an interval between 1–6 months from the index colonoscopy as an acceptable interval.[13,48]

An endoscopically invisible dysplastic lesion detected randomly during white-light endoscopy, and confirmed by a second gastroenterology pathologist, should prompt referral to an expert endoscopist skilled in surveillance using chromoendoscopy[12,48,50]. In these examinations, in addition to targeted biopsies, random biopsies should be considered to rule out presence of invisible dysplasia. Given the associated high risk of synchronous and metachronous CRC, an endoscopically invisible HGD, or multifocal LGD is an indication for colectomy[13,51].

In all cases, colectomy remains an option and risks and benefits of endoscopic resection and surveillance and colon resection should be carefully discussed. Lesions detected in histologically proven non-colitic segments of colon can be treated as sporadic adenomas and follow the standard post-polypectomy surveillance recommendations.[3,12] Pathology that is indefinite for dysplasia should prompt aggressive treatment of underlying active inflammation, followed by repeat colonoscopy, ideally with surface chromoendoscopy[13,52,53].

The presence of HGD in a completely resected dysplasia necessitates a discussion with the patient regarding risks and benefits of continuing surveillance and surgical intervention. Decisions should be made and fashioned on a case-by-case basis.[13] In IBD patients who had dysplasia on one colonoscopy followed by the absence of dysplasia on a subsequent colonoscopy does not preclude or lessens the risk of carcinoma.[3,12]

Pouch Surveillance

In patients with IBD who underwent restorative proctocolectomy (RPC) ileal pouch-anal anastomosis (IPAA), the incidence of pouch carcinoma appears to be low. No consensus exists regarding optimal patient selection for surveillance, surveillance intervals, or preferred surveillance technique. Potential risk factors presumed to be associated with higher risk of developing neoplasia after RPC and IPAA include history of dysplasia or CRC, PSC, refractory pouchitis, and type C pouch mucosa (atrophic mucosa with severe inflammation).[13,54]

A case-control, population-based study of 1200 patients with IBD and IPAA found that only history of colorectal neoplasia was associate with pouch-related neoplasia, where hazards ratio was 3.8 (95% CI, 1.4 – 10.2) for prior dysplasia, and 24.7 (95% CI, 9.6–63.4) for prior carcinoma. In this cohort, 63% of pouch carcinoma occurred in the anal transition zone.[55] In a recent systematic review and meta-analysis including 8403 pouch patients with variable duration of follow-up, the pooled prevalence of carcinoma in the IPAA was 0.5% (95% CI, 0.3%–0.6%). in another subset of patients, 7647 patients, in whom pouch dysplasia was

reported, the pooled pouch dysplasia prevalence was 0.8% (95% CI, 0.5%–1.3%). This was similarly true in studies including only high risk patients such as history of prior CRC, pouchitis, longer duration of the disease (> 8years), or PSC; (0.9%–4.6%).[7,56–58] The cumulative incidences of pouch carcinoma was found to be 0.4%, 0.9%, 1.4%, 2.7% and 3.4% after 5, 10, 15, 20, and 25 years from IPAA construction[7,55,59]. Risk factors in this systematic review were similar to the previously mentioned as above.

Patients without history of colorectal neoplasia prior to RPC and IPAA had very low incidence of pouch-related neoplasia, accounting for about 2.2% after 15 years. Thus, patients with history of dysplasia or carcinoma prior to their pouch creation should undergo *semi-annual surveillance*, while patients with history of PS and refractory pouchitis may be considered for a yearly exam. During each, surveillance biopsies should be obtained from the pouch as well as anal transition zone. There are no available data on the use and/or yield of image-enhanced endoscopy in pouch surveillance.

Surgical Management

A dysplastic lesion that is not endoscopically resectable is an indication for colectomy. Endoscopic features suggesting unresectability include ill-defined margins, features of submucosal invasion, asymmetrical lift upon submucosal injection not attributed to inflammatory induced fibrosis, overlying ulceration, large depressions, and flat neoplastic changes adjacent to the lesion. Technically challenging locations may also prompt surgery. Surgery is also indicated for endoscopically invisible high-grade dysplasia, or multifocal low grade dysplasia, recurrence after resection, or lesions removed but do not meet resectability criteria by SCENIC.

In patients with UC, colonic stricture should considered malignancy until proved otherwise, especially if thorough endoscopic evaluation cannot be performed and obtaining proper tissue samples is not feasible; in such situations surgery is also indicated.

V. Special Considerations

Mucosectomy vs. stapled anastomosis and keeping the anal transitional zone (ATZ)

The decision to choose mucosectomy with hand-sewn anastomosis versus stapled pouch-anal anastomosis with ATZ preservation is a challenging and highly debated topic. Proponents of the former advocate that mucosectomy ensures eradication of at-risk colorectal mucosa, eliminating the risk of cancer. In this technique there is significant manipulation of the anal canal during retraction with removal of the distal rectal ‘sampling’ zone. These variations often result in postoperative functional problems with higher rates of fecal seepage and incontinence[60].

In contrast, stapled IPAA is teachnically more feasable, less time-consuming, and less likely to be associated with untoward functional outcomes.[61] Stapled IPAA is performed by preserving the most distal portion of the rectum called the rectal cuff. Studies have shown that islands of retained columnar epithelial cells are retained after mucosectomy in 20% of cases.[62] Indeed, many of the described cases of pouch adenocarcinoma occur despite mucosectomy.

In our practice if no dysplasia was noted in the pathologic colorectal specimen and the patient exhibits no other risk factors (PSC, history of family CRC) then stapled IPAA is performed, followed by annual ileal pouch and ATZ biopsies with pathologic evaluation. This surveillance period may be extended to every 2–3 years if ATZ remains negative for dysplasia. Patients with dysplasia confined to colon and upper rectum without other risk factors may still be a candidate for stapled IPAA after careful counseling and discussion regarding oncologic risks and benefits. Prior to determination, the rectum is extensively biopsied throughout, and if no dysplasia exists in the lower rectum, a stapled IPAA may be offered without significant increased oncologic risk. ATZ evaluation with biopsies are done on annual basis. Presence of CRC and dysplasia in lower 2/3 of the rectum prompts mucosectomy and hand sewn anastomosis.[60] The risk of dysplastic transformation within the ileal pouch itself for IBD patients is low.[60,63]

A proposed algorithm for management of ATZ dysplasia after IPAA was recommended. For HGD in the ATZ, careful ATZ biopsies should be performed at 3–6 months intervals. If no further dysplasia is detected then annual biopsies can be carried out. However, should dysplasia persists on 2 consecutive biopsies then trans-perineal mucosectomy and pouch advancement or trans-abdominal approach could be considered for removal of the rectal cuff, or anal canal stripping for control of retained mucosa. For LGD, similar biopsies intervals are preferred. If apparent regression of dysplasia is proved, then yearly biopsies done thereafter. However, the presence of LGD for 3 (instead of 2 as in HGD) occurrences should prompt surgical intervention as above[60].

Rectal Cancer in Patients with Colitis

The treatment of stage II and III rectal cancer must involve a multidisciplinary approach for best oncologic outcomes. Neoadjuvant chemoradiotherapy has become a cornerstone in the multidisciplinary protocols subsquent studies have validated the benefits of preoperative radiation therapy in patients who do not have inflammatory bowel disease[64]. All patients with or without inflammatory bowel disease should have neoadjuvant therapy considered in certain circumstances, but especially those patients in whom a restorative procedure is considered. Adherence to strict oncologic surgical principles regarding circumferential radial margins and total mesorectal excision must be obeyed[65]. As with any type of restorative procedure, preoperative radiation avoids potential devastating functional complications associated with radiation exposure to the newly created ileal J-pouch, if appropriate for the patient's disease.

Gastrointestinal (GI) toxicity remains a challenge and occasionally results in unplanned delays and interruptions in treatment, negatively influencing local control and survival[66]. Acute GI Toxicity could be partially due to the large amount of normal small bowel that is in the standard pelvic radiation field. A dose-volume relationship between amount of small bowel exposed to/receiving low and intermittent doses of radiation and rate of severe diarrhea have been reported[67,68]. However, such short-term toxicities do not outweigh the increase in survival benefit[69].

In a retrospective analysis of 161 patients with IBD who had rectal cancer, 66 patients (41%) received pre-operative radiotherapy, including short-course (32 patients), long-course (13

patients), and chemoradiotherapy (21 patients). Grade 3 or higher GI toxicity was encountered in 0%, 7.7%, and 28.6% respectively. Grade 3 or higher toxicity was overall 28% and not associated with the type of pre-operative therapy. The authors concluded that radiotherapy does not impose excessive rates of toxicity pre-or-post-operatively in IBD patients with rectal cancer, supporting the use of standard radiotherapy protocols in IBD patients with rectal cancer[70].

Risk of cancer after colectomy

The cumulative risk of bowel surgery in patients with UC is 25%–30%, and is estimated to be 70%–80% in CD patients.[7,71,72] RPC and IPAA is considered the standard procedure of choice for UC and selected patients with indeterminate colitis. However, this procedure is usually performed over multiple operations, and the first stage being a total abdominal colectomy and end ileostomy. Patient and clinician concerns about comorbidities such as sexual and urinary function or fertility, may lead to choosing a total proctocolectomy with permanent ileostomy [7].

It has been reported that total abdominal colectomy (TAC) and ileorectal anastomosis (IRA) may be a consideration in certain patients with UC.[63] Alternatively, TAC and IRA may be the first restorative option for patients with extensive CD[63,73]. Benefits of such approach include preserved continence, as well as urinary and sexual functions. Furthermore, when fecundity is of concern, this procedure, particularly when performed laparoscopically, may decrease postoperative adhesions thereby increasing the probability of spontaneous pregnancy[63,74,75].

A systematic review and meta-analysis recently studied the risk of neoplasia after colectomy in patients with IBD. A pooled analysis of 1011 IBD patients, with a variable follow-up ranging from 0.25 – 40 years, demonstrated 2.1% prevalence of carcinoma in the retained rectal stump (95% CI, 1.3–3). However, the cumulative rectal cancer incidence in UC patients with rectal stump or IRA was evaluated in one study and shown to be 12.6% after 24 years from surgery.[76] This analysis detected no difference in carcinoma of rectal stump prevalence between UC and CD (2.2%, 95% CI, 1.3%–3.4% vs. 2.1%, 95% CI, 0.6%–4.4%)[7].

For IRA, the calculated pooled rectal carcinoma prevalence was 2.4% (95% CI, 1.7%–3.3%), and the pooled prevalence of dysplasia was 2.5% (95% CI, 1.2%–4.2%). The duration of follow -up varied from 1 to 35 years. There was lower prevalence of carcinoma in studies published after 1990. Three studies in this review reported on the cumulative incidence of rectal carcinoma in IBD patients who underwent IRA[7,77–79] The pooled analysis showed cumulative incidence of 0%, 5%, and 10% after 10, 20, and 25 years from IBD onset respectivel.[7]. One study estimated 0%, 2%, 5%, and 14% cumulative incidence of rectal carcinoma after 5, 10, 15, and 20 years from IRA construction, and 7%, 9%, 20%, and 25% for rectal dysplasia, respectively[80]. Regardless, in all situations, a detailed discussion regarding functional outcomes, risks of neoplasia, and fertility should be performed with the patient. Final decisions should be individually tailored.

VI. Personalized Medicine for colitis-associated cancer: 3D Human Models

The heterogeneity of human disease and the relative absence of in vitro models, and advances in stem cell biology have promoted the acquisition of new human based 3D models. In 2011, Sato, developed long-term in vitro cultures from murine bowel and from human colon. The cultures involved an air interface, and were able to be propagated indefinitely. These techniques have been modified, and Sato[81,82] and Kuo[83,84] now use Matrigel pillows for embedding the organoids and growth is maintained by a rich media containing R-spondin, Wnt3A, and Noggin to support the crypt units. However, these techniques were utilized for disease states, especially cancer. While the terminal state of colitis might be cancer, there are also other manifestations of the disease state which might be modeled and interrogated using such a system.

In 2015, Van Dussen[85] reported the capacity to isolate and propagate primary epithelial organoids from patients with inflammatory bowel disease. Like the techniques reported by Sato, Clevers, and Kuo, they were maintained in Matrigel pillow, and sustained in a media rich in Wnt 3A, Noggin, and R-spondin. These organoids were able to demonstrate biological activity in the face of a challenge including an E. coli bacterial interface where differential adhesion was examined. Further studies by Mokry[86] on inflammatory bowel disease used these techniques to query for risk coding by non-protein coding epigenetic elements. Here they queried a small number of organoids from patients with both Crohn's disease and ulcerative colitis, finding that some SNPs correlated with active promoting regions of the DNA, correlating with transcriptional regulation.

Our own experience with such techniques indicates that these models may be used to generate highly reproducible individualized models of patients with these diseases (Figure 2). Not only will a limited view of personalized medicine be available, but also mechanisms of in vitro and in vivo investigation will be possible using these technologies.

Research Summary

The advent of personalized medicine has arrived for multiple disease states, including cancer. Recent advances in technology now have potential to generate rapid models allowing in vitro and in silico functional data to not only better understand the disease, but to potential test preventive and therapeutic strategies on individual avatars. The models presented here are just the beginning of a new phase of investigation.

VII. Future Treatment Strategies

Current therapy is targeted non-specifically against the inflammatory condition which initiates these diseases and their malignant sequelae. Surgery to prevent the development of oncogenesis has its own set of complications. Future initiatives include personalizing treatment, perhaps using organoids from individual patients to test therapies ex vivo or even better, as targets of gene therapy to convert the colitic and oncogenetic processes to those that result in the regeneration of normal bowel. As more sophisticated strategies are available, one could indeed envision using gut flora to affect such therapeutic strategies, resulting in the recreation of normal colon.

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References

1. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut. 2001; 48(4):526–535. [PubMed: 11247898]
2. Itzkowitz SH, Harpaz N. Diagnosis and management of dysplasia in patients with inflammatory bowel diseases. Gastroenterology. 2004; 126(6):1634–1648. [PubMed: 15168373]
3. Farraye FA, Odze RD, Eaden J, et al. AGA medical position statement on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. Gastroenterology. 2010; 138(2):738–745. [PubMed: 20141808]
4. Rutter MD, Saunders BP, Wilkinson KH, et al. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. Gastroenterology. 2006; 130(4):1030–1038. [PubMed: 16618396]
5. Gillen CD, Walmsley RS, Prior P, Andrews HA, Allan RN. Ulcerative colitis and Crohn's disease: a comparison of the colorectal cancer risk in extensive colitis. Gut. 1994; 35(11):1590–1592. [PubMed: 7828978]
6. Jess T, Loftus EV Jr, Velayos FS, et al. Risk of intestinal cancer in inflammatory bowel disease: a population-based study from olmsted county, Minnesota. Gastroenterology. 2006; 130(4):1039–1046. [PubMed: 16618397]
7. Derikx LA, Nissen LH, Smits LJ, Shen B, Hoentjen F. Risk of Neoplasia After Colectomy in Patients With Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2016; 14(6):798–806. e720. [PubMed: 26407752]
8. Connelly TM, Koltun WA. The surgical treatment of inflammatory bowel disease-associated dysplasia. Expert Rev Gastroenterol Hepatol. 2013; 7(4):307–321. quiz 322. [PubMed: 23639089]
9. Ananthakrishnan AN, Cagan A, Cai T, et al. Colonoscopy is associated with a reduced risk for colon cancer and mortality in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2015; 13(2):322–329. e321. [PubMed: 25041865]
10. Huang LC, Merchea A. Dysplasia and Cancer in Inflammatory Bowel Disease. Surg Clin North Am. 2017; 97(3):627–639. [PubMed: 28501251]
11. Baars JE, Kuipers EJ, van Haastert M, Nicolai JJ, Poen AC, van der Woude CJ. Age at diagnosis of inflammatory bowel disease influences early development of colorectal cancer in inflammatory bowel disease patients: a nationwide, long-term survey. J Gastroenterol. 2012; 47(12):1308–1322. [PubMed: 22627504]
12. Itzkowitz SH, Present DH. Consensus conference: Colorectal cancer screening and surveillance in inflammatory bowel disease. Inflamm Bowel Dis. 2005; 11(3):314–321. [PubMed: 15735438]
13. Shergill AK, Lightdale JR, Bruining DH, et al. The role of endoscopy in inflammatory bowel disease. Gastrointest Endosc. 2015; 81(5):1101–1121. e1101–1113. [PubMed: 25800660]
14. Lashner BA, Turner BC, Bostwick DG, Frank PH, Hanauer SB. Dysplasia and cancer complicating strictures in ulcerative colitis. Dig Dis Sci. 1990; 35(3):349–352. [PubMed: 2307080]
15. Sartor RB. Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis. Nat Clin Pract Gastroenterol Hepatol. 2006; 3(7):390–407. [PubMed: 16819502]
16. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990; 61(5):759–767. [PubMed: 2188735]
17. Baumler AJ, Sperandio V. Interactions between the microbiota and pathogenic bacteria in the gut. Nature. 2016; 535(7610):85–93. [PubMed: 27383983]
18. Chen S, Huang EH. The colon cancer stem cell microenvironment holds keys to future cancer therapy. J Gastrointest Surg. 2014; 18(5):1040–1048. [PubMed: 24643495]
19. Burmer GC, Rabinovitch PS, Haggitt RC, et al. Neoplastic progression in ulcerative colitis: histology, DNA content, and loss of a p53 allele. Gastroenterology. 1992; 103(5):1602–1610. [PubMed: 1358743]

20. Yaeger R, Shah MA, Miller VA, et al. Genomic Alterations Observed in Colitis- Associated Cancers Are Distinct From Those Found in Sporadic Colorectal Cancers and Vary by Type of Inflammatory Bowel Disease. Gastroenterology. 2016; 151(2):278–287. e276. [PubMed: 27063727]
21. Robles AI, Traverso G, Zhang M, et al. Whole-Exome Sequencing Analyses of Inflammatory Bowel Disease-Associated Colorectal Cancers. Gastroenterology. 2016; 150(4):931–943. [PubMed: 26764183]
22. Hussain SP, Amstad P, Raja K, et al. Increased p53 mutation load in noncancerous colon tissue from ulcerative colitis: a cancer-prone chronic inflammatory disease. Cancer Res. 2000; 60(13): 3333–3337. [PubMed: 10910033]
23. Colliver DW, Crawford NP, Eichenberger MR, et al. Molecular profiling of ulcerative colitis-associated neoplastic progression. Exp Mol Pathol. 2006; 80(1):1–10. [PubMed: 16277983]
24. Romano M, FDEF, Zarantonello L, et al. From Inflammation to Cancer in Inflammatory Bowel Disease: Molecular Perspectives. Anticancer Res. 2016; 36(4):1447–1460. [PubMed: 27069120]
25. Grivennikov S, Karin E, Terzic J, et al. IL-6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. Cancer Cell. 2009; 15(2):103–113. [PubMed: 19185845]
26. Grivennikov SI, Karin M. Dangerous liaisons: STAT3 and NF-kappaB collaboration and crosstalk in cancer. Cytokine Growth Factor Rev. 2010; 21(1):11–19. [PubMed: 20018552]
27. Xiao H, Gulen MF, Qin J, et al. The Toll-interleukin-1 receptor member SIGIRR regulates colonic epithelial homeostasis, inflammation, and tumorigenesis. Immunity. 2007; 26(4):461–475. [PubMed: 17398123]
28. Yang J, Liao X, Agarwal MK, Barnes L, Auron PE, Stark GR. Unphosphorylated STAT3 accumulates in response to IL-6 and activates transcription by binding to NFkappaB. Genes Dev. 2007; 21(11):1396–1408. [PubMed: 17510282]
29. Clevers H. The Paneth cell, caloric restriction, and intestinal integrity. N Engl J Med. 2012; 367(16):1560–1561. [PubMed: 23075184]
30. Collins PD, Mpofu C, Watson AJ, Rhodes JM. Strategies for detecting colon cancer and/or dysplasia in patients with inflammatory bowel disease. Cochrane Database Syst Rev. 2006; (2):CD000279. [PubMed: 16625534]
31. Lutgens MW, Oldenburg B, Siersema PD, et al. Colonoscopic surveillance improves survival after colorectal cancer diagnosis in inflammatory bowel disease. Br J Cancer. 2009; 101(10):1671–1675. [PubMed: 19826420]
32. Soetikno R, Kaltenbach T, McQuaid KR, et al. Paradigm Shift in the Surveillance and Management of Dysplasia in Inflammatory Bowel Disease (West). Dig Endosc. 2016; 28(3):266–273. [PubMed: 26866420]
33. 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. [PubMed: 7450425]
34. East JE. Colonoscopic Cancer Surveillance in Inflammatory Bowel Disease: What's New Beyond Random Biopsy? Clin Endosc. 2012; 45(3):274–277. [PubMed: 22977816]
35. Guagnozzi D, Lucendo AJ. Colorectal cancer surveillance in patients with inflammatory bowel disease: What is new? World J Gastrointest Endosc. 2012; 4(4):108–116. [PubMed: 22523611]
36. Rutter MD. Surveillance programmes for neoplasia in colitis. J Gastroenterol. 2011; 46(Suppl 1): 1–5.
37. 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(4):880–888. [PubMed: 12671882]
38. Kiesslich R, Neurath MF. Magnifying chromoendoscopy: effective diagnostic tool for screening colonoscopy. J Gastroenterol Hepatol. 2007; 22(11):1700–1701. [PubMed: 17914935]
39. Marion JF, Waye JD, Present DH, et al. Chromoendoscopy-targeted biopsies are superior to standard colonoscopic surveillance for detecting dysplasia in inflammatory bowel disease patients: a prospective endoscopic trial. Am J Gastroenterol. 2008; 103(9):2342–2349. [PubMed: 18844620]

40. 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. [PubMed: 14724160]
41. Hurlstone DP, Sanders DS, Lobo AJ, McAlindon ME, Cross SS. Indigo carmine-assisted high-magnification chromoscopic colonoscopy for the detection and characterisation of intraepithelial neoplasia in ulcerative colitis: a prospective evaluation. Endoscopy. 2005; 37(12):1186–1192. [PubMed: 16329015]
42. Soetikno R, Subramanian V, Kaltenbach T, et al. The detection of nonpolypoid (flat and depressed) colorectal neoplasms in patients with inflammatory bowel disease. Gastroenterology. 2013; 144(7):1349–1352. 1352 e1341–1346. [PubMed: 23583483]
43. Taylor BA, Pemberton JH, Carpenter HA, et al. Dysplasia in chronic ulcerative colitis: implications for colonoscopic surveillance. Dis Colon Rectum. 1992; 35(10):950–956. [PubMed: 1395982]
44. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc. 2003; 58(6 Suppl):S3–43. [PubMed: 14652541]
45. Murthy SK, Kiesslich R. Evolving endoscopic strategies for detection and treatment of neoplastic lesions in inflammatory bowel disease. Gastrointest Endosc. 2013; 77(3):351–359. [PubMed: 23317581]
46. Allen PB, Kamm MA, De Cruz P, Desmond PV. Dysplastic lesions in ulcerative colitis: changing paradigms. Inflamm Bowel Dis. 2010; 16(11):1978–1983. [PubMed: 20803510]
47. Rutter MD, Riddell RH. Colorectal dysplasia in inflammatory bowel disease: a clinicopathologic perspective. Clin Gastroenterol Hepatol. 2014; 12(3):359–367. [PubMed: 23756224]
48. Laine L, Kaltenbach T, Barkun A, McQuaid KR, Subramanian V, Soetikno R. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. Gastroenterology. 2015; 148(3):639–651. e628. [PubMed: 25702852]
49. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008; 336(7650):924–926. [PubMed: 18436948]
50. Annese V, Daperno M, Rutter MD, et al. European evidence based consensus for endoscopy in inflammatory bowel disease. J Crohns Colitis. 2013; 7(12):982–1018. [PubMed: 24184171]
51. Zisman TL, Bronner MP, Rulyak S, et al. Prospective study of the progression of low-grade dysplasia in ulcerative colitis using current cancer surveillance guidelines. Inflamm Bowel Dis. 2012; 18(12):2240–2246. [PubMed: 22508402]
52. Pekow JR, Hetzel JT, Rothe JA, et al. Outcome after surveillance of low-grade and indefinite dysplasia in patients with ulcerative colitis. Inflamm Bowel Dis. 2010; 16(8):1352–1356. [PubMed: 20027656]
53. van Schaik FD, ten Kate FJ, Offerhaus GJ, et al. Misclassification of dysplasia in patients with inflammatory bowel disease: consequences for progression rates to advanced neoplasia. Inflamm Bowel Dis. 2011; 17(5):1108–1116. [PubMed: 20824815]
54. Liu ZX, Kiran RP, Bennett AE, Ni RZ, Shen B. Diagnosis and management of dysplasia and cancer of the ileal pouch in patients with underlying inflammatory bowel disease. Cancer. 2011; 117(14):3081–3092. [PubMed: 21264836]
55. Derikx LA, Kievit W, Drenth JP, et al. Prior colorectal neoplasia is associated with increased risk of ileoanal pouch neoplasia in patients with inflammatory bowel disease. Gastroenterology. 2014; 146(1):119–128. e111. [PubMed: 24076060]
56. Imam MH, Eaton JE, Puckett JS, et al. Neoplasia in the ileoanal pouch following colectomy in patients with ulcerative colitis and primary sclerosing cholangitis. J Crohns Colitis. 2014; 8(10): 1294–1299. [PubMed: 24768559]
57. Kuiper T, Vlug MS, van den Broek FJ, et al. The prevalence of dysplasia in the ileoanal pouch following restorative proctocolectomy for ulcerative colitis with associated dysplasia. Colorectal Dis. 2012; 14(4):469–473. [PubMed: 21689341]
58. Vento P, Lepisto A, Karkkainen P, Ristimaki A, Haglund C, Jarvinen HJ. Risk of cancer in patients with chronic pouchitis after restorative proctocolectomy for ulcerative colitis. Colorectal Dis. 2011; 13(1):58–66. [PubMed: 19832871]

59. Kariv R, Remzi FH, Lian L, et al. Preoperative colorectal neoplasia increases risk for pouch neoplasia in patients with restorative proctocolectomy. Gastroenterology. 2010; 139(3):806–812. 812 e801–802. [PubMed: 20537999]
60. Remzi FH, Fazio VW, Delaney CP, et al. Dysplasia of the anal transitional zone after ileal pouch-anal anastomosis: results of prospective evaluation after a minimum of ten years. Dis Colon Rectum. 2003; 46(1):6–13. [PubMed: 12544515]
61. Tuckson W, Lavery I, Fazio V, Oakley J, Church J, Milsom J. Manometric and functional comparison of ileal pouch anal anastomosis with and without anal manipulation. Am J Surg. 1991; 161(1):90–95. discussion 95–96. [PubMed: 1987862]
62. O'Connell PR, Pemberton JH, Weiland LH, et al. Does rectal mucosa regenerate after ileoanal anastomosis? Dis Colon Rectum. 1987; 30(1):1–5. [PubMed: 3803100]
63. Borjesson L, Willen R, Haboubi N, Duff SE, Hulten L. The risk of dysplasia and cancer in the ileal pouch mucosa after restorative proctocolectomy for ulcerative proctocolitis is low: a long-term term follow-up study. Colorectal Dis. 2004; 6(6):494–498. [PubMed: 15521942]
64. Cedermark B, Dahlberg M, et al. Swedish Rectal Cancer T. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med. 1997; 336(14):980–987. [PubMed: 9091798]
65. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. Lancet. 1993; 341(8843):457–460. [PubMed: 8094488]
66. Fietkau R, Rodel C, Hohenberger W, et al. Rectal cancer delivery of radiotherapy in adequate time and with adequate dose is influenced by treatment center, treatment schedule, and gender and is prognostic parameter for local control: results of study CAO/ARO/AIO-94. Int J Radiat Oncol Biol Phys. 2007; 67(4):1008–1019. [PubMed: 17197130]
67. Robertson JM, Lockman D, Yan D, Wallace M. The dose-volume relationship of small bowel irradiation and acute grade 3 diarrhea during chemoradiotherapy for rectal cancer. Int J Radiat Oncol Biol Phys. 2008; 70(2):413–418. [PubMed: 17904305]
68. Tho LM, Glegg M, Paterson J, et al. Acute small bowel toxicity and preoperative chemoradiotherapy for rectal cancer: investigating dose-volume relationships and role for inverse planning. Int J Radiat Oncol Biol Phys. 2006; 66(2):505–513. [PubMed: 16879928]
69. Chang BW, Kumar AM, Koyfman SA, Kalady M, Lavery I, Abdel-Wahab M. Radiation therapy in patients with inflammatory bowel disease and colorectal cancer: risks and benefits. Int J Colorectal Dis. 2015; 30(3):403–408. [PubMed: 25564345]
70. Bosch SL, van Rooijen SJ, Bokkerink GM, et al. Acute toxicity and surgical complications after preoperative (chemo)radiation therapy for rectal cancer in patients with inflammatory bowel disease. Radiother Oncol. 2017; 123(1):147–153. [PubMed: 28291546]
71. Andersson P, Soderholm JD. Surgery in ulcerative colitis: indication and timing. Dig Dis. 2009; 27(3):335–340. [PubMed: 19786761]
72. Martin ST, Vogel JD. Restorative procedures in colonic crohn disease. Clin Colon Rectal Surg. 2013; 26(2):100–105. [PubMed: 24436657]
73. Lofberg R, Liljeqvist L, Lindquist K, Veress B, Reinholt FP, Tribukait B. Dysplasia and DNA aneuploidy in a pelvic pouch. Report of a case. Dis Colon Rectum. 1991; 34(3):280–283. discussion 283–284. [PubMed: 1999138]
74. Gullberg K, Stahlberg D, Liljeqvist L, et al. Neoplastic transformation of the pelvic pouch mucosa in patients with ulcerative colitis. Gastroenterology. 1997; 112(5):1487–1492. [PubMed: 9136826]
75. Sarigol S, Wyllie R, Gramlich T, et al. Incidence of dysplasia in pelvic pouches in pediatric patients after ileal pouch-anal anastomosis for ulcerative colitis. J Pediatr Gastroenterol Nutr. 1999; 28(4):429–434. [PubMed: 10204509]
76. Johnson WR, Hughes ES, McDermott FT, Pihl EA, Katrivessis H. The outcome of patients with ulcerative colitis managed by subtotal colectomy. Surg Gynecol Obstet. 1986; 162(5):421–425. [PubMed: 3704893]
77. Andersson P, Norblad R, Soderholm JD, Myrelid P. Ileorectal anastomosis in comparison with ileal pouch anal anastomosis in reconstructive surgery for ulcerative colitis--a single institution experience. J Crohns Colitis. 2014; 8(7):582–589. [PubMed: 24315777]

78. Grundfest SF, Fazio V, Weiss RA, et al. The risk of cancer following colectomy and ileorectal anastomosis for extensive mucosal ulcerative colitis. Ann Surg. 1981; 193(1):9–14. [PubMed: 7458456]

79. Baker WN, Glass RE, Ritchie JK, Aylett SO. Cancer of the rectum following colectomy and ileorectal anastomosis for ulcerative colitis. Br J Surg. 1978; 65(12):862–868. [PubMed: 737423]

80. da Luz Moreira A, Kiran RP, Lavery I. Clinical outcomes of ileorectal anastomosis for ulcerative colitis. Br J Surg. 2010; 97(1):65–69. [PubMed: 20013930]

81. Sato T, Stange DE, Ferrante M, et al. Long-term expansion of epithelial organoids from human colon, adenoma, adenocarcinoma, and Barrett's epithelium. Gastroenterology. 2011; 141(5):1762–1772. [PubMed: 21889923]

82. Sugimoto S, Sato T. Establishment of 3D Intestinal Organoid Cultures from Intestinal Stem Cells. Methods Mol Biol. 2017; 1612:97–105. [PubMed: 28634937]

83. Li X, Nadauld L, Ootani A, et al. Oncogenic transformation of diverse gastrointestinal tissues in primary organoid culture. Nat Med. 2014; 20(7):769–777. [PubMed: 24859528]

84. Yan KS, Janda CY, Chang J, et al. Non-equivalence of Wnt and R-spondin ligands during Lgr5+ intestinal stem-cell self-renewal. Nature. 2017; 545(7653):238–242. [PubMed: 28467820]

85. VanDussen KL, Marinshaw JM, Shaikh N, et al. Development of an enhanced human gastrointestinal epithelial culture system to facilitate patient-based assays. Gut. 2015; 64(6):911–920. [PubMed: 25007816]

86. Mokry M, Middendorp S, Wiegerinck CL, et al. Many inflammatory bowel disease risk loci include regions that regulate gene expression in immune cells and the intestinal epithelium. Gastroenterology. 2014; 146(4):1040–1047. [PubMed: 24333384]

KEYPOINTS

- Colitis-associated cancer is a complex disease process for which the pathogenesis is unclear.
- Advanced colonoscopic techniques are the standard of care for surveillance of those patients with colitis. Unique pathology mandates close surveillance and multidisciplinary discussion.
- When proctocolectomy is deemed necessary, specialized considerations for restorative procedures and surveillance are required.
- Novel model systems for providing personalized medicine and for understanding pathogenesis include colonic organoids.

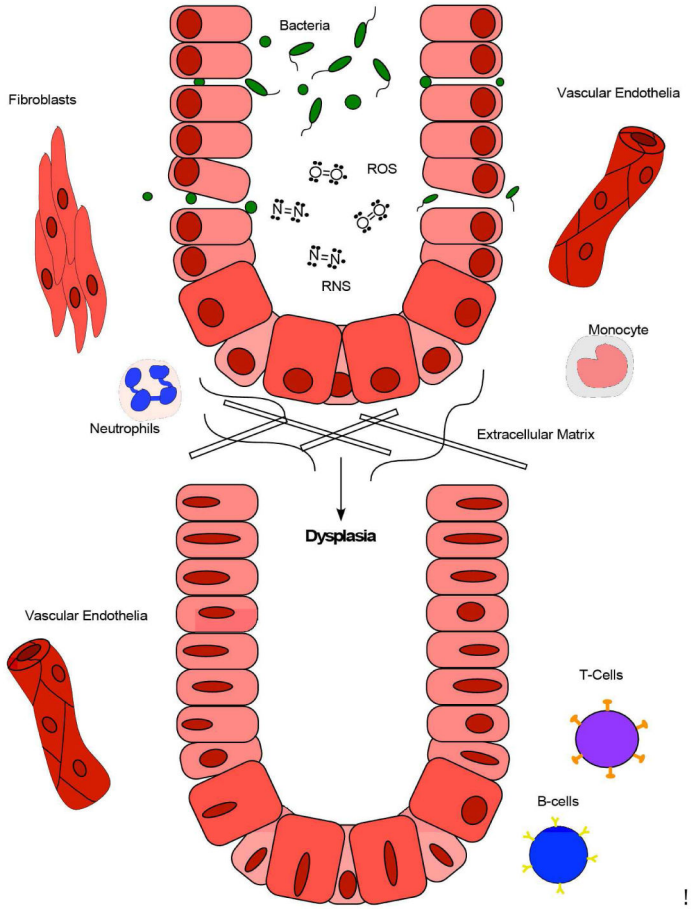

Figure 1. The colitic microenvironment

The pathogenesis of colitis involves elements of the microenvironment, co-opted in the progression to dysplasia and cancer. Interactions initiated by the inflammatory process result in the creation of reactive oxygen (ROS) and reactive nitrogen species (RNS). Early intravasation of neutrophils, and vasculature give way to chronic influences of fibroblasts, myeloid cells, and T-cells. During the acute phase, loss of intercellular adhesion results in leakiness that allows penetration of bacteria into the submucosa with immune responses. *Courtesy of* Jennifer Stiene

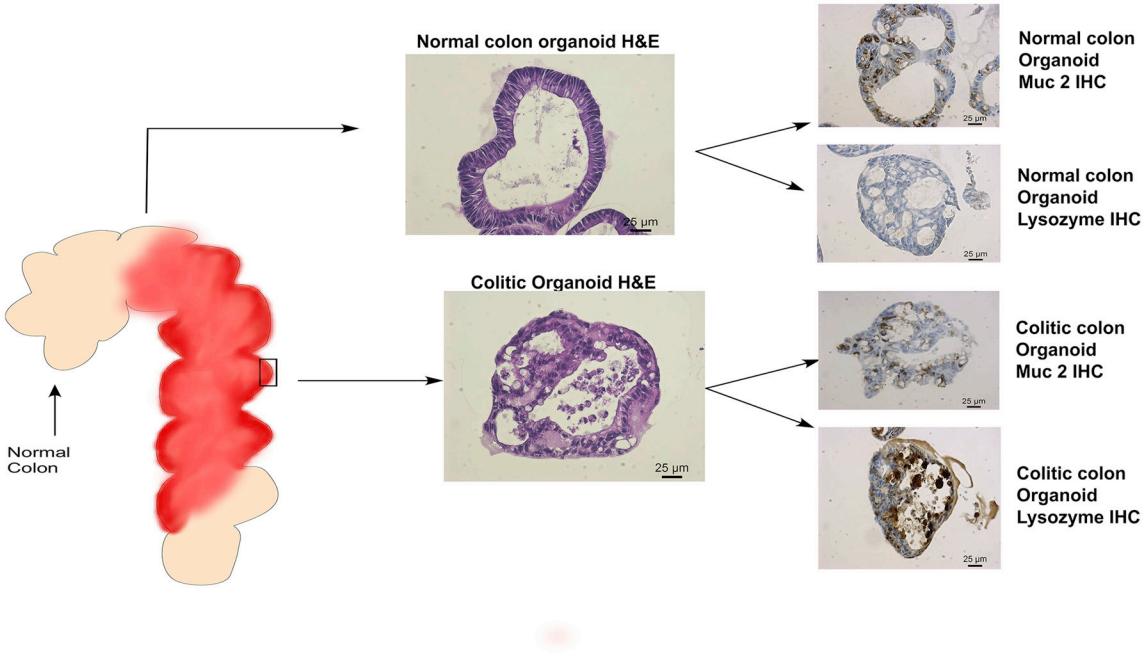

Figure 2. A new model to interrogate colitis: the colitic organoid

Recent advances in stem cell biology have resulted in methodology to isolate and propagate primary colonic tissues in vitro. A. Normal colon organoid with simple epithelia, mucin secretion (MUC2) and lack of lysozyme, a marker for the niche initiator cell, the Paneth cell. B. Colitic colon organoid, bearing a stratified epithelium, relative lack of mucin secretion (MUC2) and increased lysozyme. In this case colitic process initiates a regenerative cue, and the niche initiating cells, Paneth cells, are marked by the stain for lysozyme. IHC = immunohistochemistry

Courtesy of Jennifer Stiene