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Colonoscopy Withdrawal Time And Dysplasia Detection In Patients With Inflammatory Bowel Disease

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Colonoscopy Withdrawal Time and Dysplasia Detection in Patients with
Inflammatory Bowel Disease

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by
Chandler McMillan
2024
COLONOSCOPY WITHDRAWAL TIME AND DYSPLASIA DETECTION IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Abstract

Compared to the general population, patients with inflammatory bowel disease (IBD) are more at risk for developing colorectal dysplasia and neoplasia in their lifetime. Given this increased risk, current guidelines recommend that patients with IBD involving at least one-third of the colon undergo routine surveillance colonoscopy exams every one to five years to monitor disease activity and severity. Colonoscopy withdrawal time (CWT) is considered an important predictor of adenoma detection and a quality metric of colonoscopy within the general population. Society organizations including the American
Society for Gastrointestinal Endoscopy and the American College of Gastroenterology have proposed a minimum average CWT of six minutes for optimal detection of dysplastic and neoplastic lesions, though recent studies have proposed to aim for a CWT of eight to nine minutes. While several CWT cutoffs have been proposed within the general population, the ideal CWT in patients with IBD has not been determined. We aimed to identify the optimal CWT associated with the detection of polypoid dysplasia in patients with IBD.

This is a single-center, retrospective study from 6/1/2017-9/1/2022 of adult subjects with IBD in endoscopic remission undergoing surveillance via high-definition white light colonoscopy. We included subjects ≥18 years of age with a confirmed diagnosis of IBD involving the colon for at least eight years, or a confirmed diagnosis of IBD and comorbid primary sclerosing cholangitis. We excluded subjects with incomplete colonoscopy, subjects with prior ileocolonic or colonic resections, and colonoscopy exams with chromoendoscopy. The primary outcome was the association between CWT and polypoid dysplasia detection. We also sought to identify an optimal CWT cutoff associated with polypoid dysplasia detection. Continuous variables were analyzed using an unpaired student’s t-test and categorical variables were analyzed using a chi-square test. Multivariate analyses were performed to assess factors associated with polypoid dysplasia.

A total of 259 subjects (mean age 56 ± 14.8 years; 51.3% female, 68% with UC; 8.9% with primary sclerosing cholangitis) underwent 330 colonoscopies. The median CWT in the study cohort was 22 minutes [interquartile range (IQR) 15-29].
Polypoid dysplasia was detected in 17.3% (n=57) of procedures. Compared to subjects without polypoid dysplasia, subjects with polypoid dysplasia were more likely to be older (p<0.001) and have a personal history of polypoid dysplasia (p<0.001) and invisible dysplasia (p=0.023). The mean CWT was significantly longer in the polypoid dysplasia group at 26 minutes (IQR 20-38.5) vs. 21 minutes (IQR 15-28) in procedures without polypoid dysplasia (p<0.001). On multivariable analysis, increased age (p < 0.001), increased CWT (p=0.001), and personal history of polypoid dysplasia (p=0.013) were independently associated with the detection of polypoid dysplasia.

A CWT of ≥ 15 minutes [odds ratio (OR) 2.71, 95% CI: 1.11-6.6; p=0.02] and not ≥ 9 minutes (OR 2.57, 95% CI: 0.33-20.2; p=0.35) is significantly associated with detection of polypoid dysplasia.

CWT did independently correlate with polypoid dysplasia detection for patients with IBD undergoing surveillance via high-definition white light colonoscopy. Specifically, a mean CWT of ≥ 15 minutes was independently associated with the detection of polypoid dysplasia, while a mean CWT of ≥ 9 minutes was not. Moving forward, future prospective studies are needed to corroborate the findings of this study.
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Introduction

Pathogenesis of IBD

Inflammatory bowel disease (IBD) is comprised of Crohn’s disease (CD), ulcerative colitis (UC), and indeterminate colitis, all chronic relapsing and remitting diseases that can impose a lifelong burden to the individual and society at large.\(^1\) It is estimated that approximately two million North Americans live with IBD, and it is projected that four million people will be living with IBD by 2030.\(^2\) The etiology of IBD is multifactorial, resulting from a complex interaction of genetic, environmental, and host-related factors that altogether contribute to chronic inflammation within the gastrointestinal tract.\(^3\) The genetic components of IBD have been well-studied, with evidence showing up to 58% concordance of CD between monozygotic twins, and a five-fold increase in the risk of developing IBD among first-degree relatives of patients with IBD.\(^4,5\) Additionally, over 200 genetic mutations have been potentially linked to the onset of IBD, suggesting that the development is polygenic in nature.\(^6\) Well-known environmental risk factors attributed to the development of IBD include smoking, diet, medications, geographic location, as well as social and psychological stressors.\(^7\) Related to the host, gut microbiota are essential to the overall health and functioning of the gastrointestinal tract, while disease states can result in the case of abnormal host immune responses to the gut microbiota.\(^8\) Dysbiosis is well defined in IBD with a known decrease in diversity of the microbiome with decreases in protective microorganisms and increases in pro-inflammatory organisms.\(^9\)
Presentations of IBD

All three forms of IBD can present similarly with symptoms of abdominal pain, diarrhea, bloody stools, and/or weight loss, though CD and UC typically have distinctive clinical characteristics and patterns of inflammation.

Crohn’s Disease manifests as discontinuous areas of inflammation and/or ulceration with areas of intervening normal mucosa ("skip lesions") that can present anywhere in the gastrointestinal tract from the mouth to the anus. The symptoms associated with CD depend on the location and extent of active inflammation within the GI tract. The classic presentation of CD includes abdominal pain, watery diarrhea, and weight loss. While watery diarrhea is a common presentation, CD can also present with bloody diarrhea, more often in patients with colonic inflammation. Presentations of abdominal pain are often colicky in nature, and can be ongoing for years prior to diagnosis. Episodes of pain may present acutely, but can also develop more gradually and present as pain flares with periods of remission in between. In some cases, pain episodes may be relieved with defecation. Involvement of the terminal ileum (the most distal portion of the small intestines) is common; thus pain can frequently localize to the right lower abdominal quadrant.

The pattern of inflammation in CD is transmural (e.g., spanning the full thickness of the bowel wall) and pathology may display evidence of granulomas on biopsies. The Montreal Classification for Inflammatory Bowel Disease is used to objectively classify the severity and extent of inflammation. It classified CD into three categories: non-stricturing non-fistulizing disease (B1), stricturing disease (B2), and fistulizing disease (B3). The formation of strictures or narrowings throughout the GI tract become
symptomatic once the lumen is significantly narrowed, with resultant obstructive features including abdominal pain, nausea, and vomiting.\textsuperscript{3} Inflammation can penetrate nearby organs, with fistula formation developing between the bowel and adjacent structures including other portions of bowel, the bladder, skin, and vagina. Fistulas can be clinically asymptomatic but may result in drainage of intestinal contents into surrounding organs.\textsuperscript{10} Roughly 25% of patients have perianal complications of CD, including perianal skin tags, abscesses, fissures, fistulae, and stenosis.\textsuperscript{3,10} Patients with CD can also experience extraintestinal manifestations of the disease, most commonly affecting the joints, skin, bone, eyes, kidney, and liver.\textsuperscript{3} The most common extraintestinal manifestation is arthritis, affecting up to 25% of patients with CD.\textsuperscript{10}

\textit{Ulcerative colitis} is characterized by inflammation limited to the colonic mucosa, extending proximally from the rectum in a continuous fashion. The Montreal Classification for Inflammatory Bowel Disease stratifies UC into three location segments: proctitis (inflammation confined to the rectum), left-sided colitis (inflammation extending from the rectum up to the splenic flexure), and pancolitis (inflammation extending beyond the splenic flexure, potentially through the entire colon).\textsuperscript{12} Symptoms of UC include urgency, increased frequency of stools, fatigue, incontinence, nocturnal bowel movements, abdominal pain, and cramping.\textsuperscript{13} Rectal bleeding is a classic symptom reported by over 90% of patients, and the severity of bleeding correlates with disease severity.\textsuperscript{14} Rectal inflammation is associated with frequent, small-volume bowel movements (i.e. tenesmus) as well as associated mucus and commonly blood in stools.\textsuperscript{3} Diarrhea results from the inability of the inflamed colon to reabsorb water, its primary job, resulting in rapid transit of the luminal contents, which often occurs postprandially
and nocturnally. Additional systemic symptoms including fever and weight loss can present with advanced disease.

Extraintestinal manifestations can present in a third of patients with UC, with peripheral arthritis also being the most common. Patients with UC and CD may develop primary sclerosing cholangitis (PSC), a scarring inflammatory condition that affects the bile ducts. Advanced PSC can result in portal hypertension, cirrhosis, and ultimately liver failure. Additionally, concomitant PSC in colitis patients can increase the risk of colorectal cancer four-to-five fold. Other complications of UC can include fulminant colitis or toxic megacolon, which can produce severe bleeding episodes and potentially be a precursor to colonic perforation; thus these conditions often require emergent surgery.

*Indeterminate colitis* is defined as “patients with colonic disease who cannot be classified into one of the two major forms of IBD.” Patients with indeterminate colitis have disease that is confined to the colon, and can present with symptoms characteristic of both CD and UC. Indeterminate colitis is generally considered a temporary diagnosis and efforts should be made to continue re-assessing these patients as some may be re-classified as CD or UC over time.

*Diagnosis of IBD*

The diagnosis of IBD is based on a combination of the clinical history, starting with a thorough history and physical exam, laboratory tests, endoscopic and histologic evaluation, and/or diagnostic imaging for confirmation.
Laboratory Testing

All patients being evaluated for a diagnosis of IBD require blood testing, including a complete blood count, basic metabolic profile, liver function tests, inflammatory markers, and stool microbiological testing to evaluate for infectious causes and/or acute inflammation. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are two biomarkers that can be measured within the blood to determine the presence of acute inflammation in the body. They are not specific for inflammation in the intestines; thus they are less useful for establishing a new diagnosis of IBD and are more helpful for monitoring ongoing IBD activity. CRP is one of the most sensitive biomarkers for inflammation, and has a high negative predictive value; a CRP level within 5 mg/dL has been linked to a less than 1% chance of active inflammatory disease. It is important to note that a negative CRP test does not necessarily exclude active inflammation; approximately 15% of patients with IBD will fail to mount a CRP response, and CRP sensitivity may vary based on disease subtype.

Non-invasive stool biomarkers such as fecal calprotectin (FCP) are more sensitive and specific for colonic inflammation. FCP is a protein measurable within the stool that conveys neutrophilic levels within the intestines. It is a direct marker of colonic mucosal inflammation and appears to be the most sensitive inflammatory biomarker, with a diagnostic sensitivity of 94% and specificity of 64% for detecting active inflammation. While an elevated FCP is sensitive for active inflammation, similar to all fecal tests it cannot discriminate between different types of inflammation. For this reason, elevated FCP levels have limited diagnostic value, while low levels of FCP make the diagnosis of IBD unlikely.
Several autoantibodies have been described in patients with UC and CD. Positive perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) are linked to UC and found in approximately 50-60% of patients.\textsuperscript{23} It can be helpful to differentiate CD from UC, particularly when considering surgical treatment options, but it is not often used as a routine diagnostic marker given its relatively low sensitivity.\textsuperscript{14,24} Anti-\textit{Saccharomyces cerevisiae} antibodies (ASCA) have been detected in approximately 40-70% of patients with CD.\textsuperscript{25} Higher levels of ASCA have been linked to a more complicated disease course in patients with CD, including the presence of fibrostenotic or perforating disease and requiring future small-bowel surgery.\textsuperscript{26}

Bloodwork evaluation may be normal, but more severe presentations of IBD, may show evidence of anemia, hypoalbuminemia, thrombocytosis, leukocytosis, an elevated CRP level, and elevated FCP.\textsuperscript{14,27}

\textit{Endoscopic Evaluation}

Endoscopy with biopsies is the primary modality for diagnosing IBD. Upper endoscopy is not routinely performed in adults as part of the diagnostic evaluation in the absence of upper gastrointestinal symptoms but should be performed if upper GI symptoms are present to assess for upper gastrointestinal CD. Colonoscopy with intubation of the terminal ileum is recommended in the workup for IBD. In addition to biopsying areas of obvious inflammation during colonoscopy, random biopsies are taken throughout various segments of the colon (terminal ileum, ascending, transverse, descending, sigmoid colon, rectum) from normal-appearing tissue to determine the histologic extent of intestinal inflammation.\textsuperscript{3} The endoscopic and histologic pattern of
disease can help to differentiate between UC, CD, and other inflammatory enteropathies. Classic endoscopic mucosal findings for both UC and CD include loss of vascularity, erythema, granularity, friability, bleeding, erosions, ulcers, and pseudopolyps. In cases of CD, there may be additional findings of aphthous ulcers and cobblestoning.

Several endoscopic scoring systems have been created for both UC and CD to determine the extent and severity of inflammation. These scoring systems include the modified Mayo UC Endoscopic Subscore (MES), the UC Endoscopic Index of Severity (UCEIS), the CD Endoscopic Index of Severity (CDEIS), the Simple Endoscopic Score for CD (SES-CD), and the Rutgeerts Postoperative Endoscopic Index for patients with postoperative CD. The most commonly used scoring system for assessment of UC severity is the MES, with a score range of zero to three. A score of zero represents no signs of inflammation; a score of one is considered mild inflammation, with evidence of erythema; a score of two represents moderate inflammation, also with evidence of friability or erosions; a score of three is considered severe inflammation, also with evidence of spontaneous bleeding or ulceration. The SES-CD is commonly used for assessment of CD. The SES-CD scoring system ranges from 0-56, and evaluates the presence and size of ulcers, the extent of the ulcerated surface, the extent of the affected disease surface, and the presence and severity of narrowings across five different intestinal segments (ileum, right colon, transverse colon, sigmoid and left colon, rectum). Higher scores for each scoring system correlate with more severe disease activity.

There are histologic findings that are characteristic for UC and CD. Findings favoring UC include diffuse crypt architectural distortion and atrophy, villous mucosal
surface, diffuse transmucosal inflammation, the absence of ileal involvement, and the presence of the cryptitis and crypt abscesses.\textsuperscript{30,31} Histologic features favoring CD include epithelioid granulomas, focal chronic inflammation within the lamina propria, focal crypt distortion, ileal involvement, and a normal mucosal surface.\textsuperscript{30,31} While both UC and CD have distinctive histologic features, factors including suboptimal clinical details and sampling, early IBD, and overlapping microscopic features can make it challenging to subclassify IBD.\textsuperscript{31}

\textit{Diagnostic Imaging}

Endoscopy assesses the extent of upper GI, ileal and colonic inflammatory disease, but it is limited in assessing disease patterns in the remaining small intestines. Diagnostic imaging modalities including Magnetic Resonance Enterography (MRE) and Computed Tomography Enterography (CTE) are often employed to assess small bowel inflammation. These studies involve ingesting contrast material to distend the small bowel in efforts to better visualize intraluminal disorders including inflammation, strictures, ulcers, and cobblestoning.\textsuperscript{3} Another non-invasive imaging modality that is used to assess the small bowel is wireless video capsule endoscopy for patients without prior surgery, known or suspected small bowel obstruction; it is thought that capsule endoscopy may improve the classification of the type of IBD and disease extent.\textsuperscript{19}

\textit{Management of IBD}

The goals of medical therapy in patients with IBD is to induce steroid-free clinical remission, biochemical remission, followed by endoscopic remission in order to avoid
complications, including the need for surgical intervention, and decrease disability and improve quality of life.\textsuperscript{32}

For management of CD, significant advancements in medical treatment have been made over the years. Current medical therapies used to manage CD include 5-aminosalicylates (5-ASA), corticosteroids, immunomodulators, biologic therapies, small molecule agents, and antibiotics. 5-ASA can be effective for treating symptoms of mild colonic CD, though oral mesalamine (5-ASA medication) has not consistently been shown to induce remission and mucosal healing in patients with active CD compared to placebo.\textsuperscript{33}

Corticosteroids do not maintain remission, and are reserved for short-term courses to treat symptom flare-ups and for bridging patients to more effective long-term medical therapies.\textsuperscript{34} Oral corticosteroids such as prednisone can be used in the short-term for management of symptomatic moderate-to-severe CD.\textsuperscript{35} Despite providing symptomatic relief, systemic corticosteroids do not reliably achieve mucosal healing.\textsuperscript{33} They are also associated with several potential adverse effects including an increased risk of intestinal perforation; thus their use should be limited when possible. While topical corticosteroids such as budesonide (i.e., Entocort) have been used for treatment of distal inflammation in CD, data showing this to be beneficial is limited.\textsuperscript{33}

Immunomodulators such as thiopurines (e.g., azathioprine, 6-mercaptopurine) and methotrexate are often used as adjunctive therapies given other available treatment options that are more effective, faster acting and safer.\textsuperscript{33} In patients with moderate-to-severe CD, immunomodulators have been shown to be an effective adjunctive therapy to anti-tumor necrosis factor (TNF) agents such as infliximab (Remicade, Renflexis,
Inflectra, Avsola, etc.) as the combination can reduce the need for corticosteroids and reduce the rate of developing anti-drug antibodies against anti-TNF agents.33

Biologic therapies encompass monoclonal antibodies such as anti-TNF, anti-integrin, and anti-interleukin (12/23p40 and anti-IL23) agents for the management of CD. Current guidelines recommend the use of anti-TNF agents such as infliximab (Remicade), adalimumab (Humira), and certolizumab pegol (Cimzia) for management of CD refractory to corticosteroids as well as thiopurines or methotrexate.36–38 Use of infliximab with thiopurines has been shown to be more effective for management of CD in patients naïve to these therapies compared to treatment with either infliximab or immunomodulators alone.39 Regarding anti-integrin therapies such as vedolizumab (Entyvio), there is strong evidence to suggest that the use of vedolizumab with or without an immunomodulator for management of moderate-to-severe CD is better than placebo and effective in inducing clinical remission in patients with CD.33 Lastly, ustekinumab (Stelara) and Risankizumab (Skyrizi) are anti-interleukin agents that can be utilized to treat moderate-to-severe CD. There is strong evidence to support the use of ustekinumab in patients with moderate-to-severe CD who have not responded to corticosteroids, immunomodulators, or anti-TNF agents, or are naïve to anti-TNF agents.40

Small molecule agents for the management of CD include upadacitinib (Rinvoq), an oral selective Janus kinase (JAK)-inhibitor approved for the treatment of the moderate-to-severe CD in patients with inadequate response or intolerance to anti-TNF agents.41 Studies have found upadacitinib to be effective in achieving and maintaining clinical remission as well as endoscopic response in patients with moderate-to-severe CD.41
Antibiotic use for CD is limited to treating complications such as abscesses and fistulas.\textsuperscript{33} Surgical intervention is often required for management of fistulas, abscesses, and perianal disease.\textsuperscript{34} Other indications include strictures, perforation, obstruction, resistant disease, dysplasia, and neoplasia.\textsuperscript{42} Up to 57\% of patients with CD require at least one surgery in their lifetime, and some patients with CD confined to the ileocecal region opt for early resection in efforts to minimize adverse effects of medical therapies.\textsuperscript{43,44}

The management of UC employs 5-ASA derivatives in addition to short-term courses of corticosteroids, immunomodulators, biologic therapies and small molecule agents. Management with 5-ASA is first-line for patients with mild-to-moderate UC. It can be administered in the form of a suppository, enema, or oral formulation, with evidence that there does not appear to be a difference in safety or efficacy among the different formulations.\textsuperscript{45} Patient’s with proctitis can be managed with 5-ASA suppositories since it can directly target the area of active inflammation.\textsuperscript{46} Patients with left-sided colitis can be managed with 5-ASA enemas in lieu of suppositories to allow for penetration of the splenic flexure, and patients with left-sided or extensive disease should be started on oral and topical 5-ASA to induce remission.\textsuperscript{46} Patients may see a response to 5-ASA drugs within two weeks, but it may take up to eight weeks to achieve symptom-free clinical remission; patients who have achieved clinical remission with 5-ASA may remain on it for maintenance.\textsuperscript{46}

Patients who have not achieved a clinical remission on 5-ASA therapies may be managed with short courses of corticosteroids while transitioning to a long-term, steroid-free medication. Rectal corticosteroids can be trialed as an adjunctive therapy to 5-ASA
drugs to induce remission in patients with proctitis or left-sided UC while oral
corticosteroids are utilized for those with more extensive disease. Response to
corticosteroids such as prednisone should be seen within two weeks before starting a
steroid taper. As previously mentioned, corticosteroids are not used for maintenance of
remission given their adverse effect profile and limited long-term efficacy. Patients who
require at least two steroid courses within a year or who cannot effectively taper off of
steroids require a switch in treatment to a more advanced therapy.

Patients with moderate-to-severe UC are managed with thiopurines, biologic
therapies or small molecule agents. Thiopurines (azathioprine or 6-mercaptopurine) are
used for patients with steroid-dependent moderate-to-severe disease in efforts to maintain
remission. Anti-TNF drugs are also effective for inducing and maintaining remission in
patients with moderate-to-severe UC. Infliximab is the most widely used anti-TNF agent
to induce and maintain remission in moderate-to-severe UC, and is followed by
adalimumab (Humira) and golimumab (Simponi). It is also often used for patients
hospitalized with severe UC flares. Similar to management in CD, patients with UC
may be managed with a combination of immunomodulator and biologic therapies to
achieve clinical and endoscopic remission. Vedolizumab is another biologic therapy
considered to be a first-line safe and effective drug for the induction of remission in
moderate-to-severe UC. Guidelines also recommend the continuation of vedolizumab to
maintain remission for patients who have successfully induced remission with
vedolizumab. Lastly, ustekinumab and most recently mirakizumab have been shown to
be more effective than placebo for induction and maintenance of remission in both
biologic naïve patients and patients with previous treatment failure with biologic agents.
Upadacitinib and tofacitinib (Xeljanz) are small molecule agents approved for the management of patients with moderate-to-severe UC.\textsuperscript{52} Tofacitinib is a non-selective JAK-inhibitor whereas upadacitinib is a selective JAK-inhibitor. Tofacitinib is effective for induction and maintenance of remission in patients with moderate-to-severe UC, and has proven to be an effective therapeutic option for patients who have previously failed anti-TNF therapies.\textsuperscript{50,52} Upadacitinib has been recently approved for the treatment of moderate-to-severe UC in patients who have had inadequate response or intolerance to one or more anti-TNF agents, and is effective for induction and maintenance of remission.\textsuperscript{52} A recent study assessing clinical response to upadacitinib in patients with prior exposure to tofacitinib found upadacitinib to be effective in achieving clinical remission in patients who have failed previous therapies.\textsuperscript{52} In addition to the use of small molecule agents, sphingosine receptor inhibitors such as ozanimod (Zeposia) and etrasimod (Velsipity) have been approved for treatment of moderate-to-severe UC and are also deemed safe and effective for induction and maintenance of clinical remission.\textsuperscript{53}

Acute severe UC (ASUC) is defined as six or more bloody bowel movements per day with at least one of the following: pulse >90 beats per minute, temperature >37.8°C, hemoglobin <10.5 g/dL, or ESR >30 mm/h.\textsuperscript{13} Patients with ASUC are often admitted to the hospital and initially managed with intravenous (IV) corticosteroids. Patients who do not respond to IV corticosteroids within three to five days are often transitioned to rescue medical therapy with biologic agents such as infliximab.\textsuperscript{13} If patients fail to respond to both corticosteroids and infliximab, early studies suggest a potential benefit from a trial with a JAK-inhibitor, otherwise, a colectomy should be performed.\textsuperscript{13}
Other indications for surgical intervention for patients with UC include uncontrolled bleeding, perforation, and dysplasia or CRC that cannot be removed endoscopically.\textsuperscript{54} It is also indicated in refractory ASUC or cases of UC refractory to medical management.\textsuperscript{54}

Disease activity monitoring for patients with CD and UC includes monitoring with serum inflammatory markers and routine surveillance colonoscopy. In patients with CD, there is evidence to suggest that monitoring FCP has prognostic value, given elevated FCP levels correlate with increased probability of relapse.\textsuperscript{55,56} Low CRP values in patients with CD are linked to reduced likelihood of clinical relapse, and high CRP values at the time of anti-TNF therapy discontinuation for patients with CD correlate with an increased likelihood of clinical relapse.\textsuperscript{57–59} In patients with UC, tracking CRP, ESR, and FCP levels may correlate with endoscopic activity, though tracking FCP levels is most sensitive for UC.\textsuperscript{22,60} Routine surveillance colonoscopy can also be used to assess for disease control and endoscopic remission. Endoscopic remission is commonly defined as an MES \(\leq 1\) for patients with UC, and an SES-CD \(<2\) or CDEIS \(<3\) with a lack of ulcerations for patients with CD.\textsuperscript{55} Endoscopic remission is an important target for both UC and CD, predicting sustained clinical remission, lower hospitalization rates, and reduced likelihood of surgical intervention.\textsuperscript{61} For patients with UC, histologic remission (i.e., absence of inflammation or structural changes within the colonic mucosa) has emerged as a treatment target in addition to endoscopic remission, with evidence to suggest that it may predict long-term remission and prevent cancer formation.\textsuperscript{62}
Colorectal Cancer Statistics

Colorectal cancer (CRC) is the third leading cause of cancer-related mortality in both men and women in the United States (US).\textsuperscript{63} The American Cancer Society estimates that the rate of CRC diagnosis has declined over the last three decades in light of more people undergoing routine CRC screening and overall improvements to lifestyle habits related to CRC development.\textsuperscript{63} While the incidence of CRC has declined by roughly 1\% each year from 2011 to 2019 in older adults, the incidence rates of CRC have been on the rise in young adult populations, increasing 1-2\% each year since the 1990s.\textsuperscript{63}

Patients with IBD are at an increased risk of developing CRC compared to the general population, and the risk of CRC is even higher in patients with IBD and concomitant PSC.\textsuperscript{64,65,66} In the next section, we detail the molecular pathways contributing to CRC development in the general population and in patients with IBD.

Colorectal Cancer Molecular Pathways

The molecular pathogenesis of CRC is a multistep process of specific mutations that transform normal colonic epithelium to invasive cancer. The first step in CRC tumor pathogenesis is the development of polyps. Polyps can be either hyperplastic, which are not pre-cancerous, or adenomatous, which are pre-cancerous. This distinction is important to make when assessing an individual’s potential to develop malignancy.\textsuperscript{67} Adenomatous polyps, or adenomas, are further classified as tubular, villous, or tubulovillous. Adenomas arise when DNA repair mechanisms are compromised, resulting in abnormal cell proliferation. Over time, adenomas can increase in size, become more dysplastic, and develop into a malignancy.\textsuperscript{68}
There are at least three major molecular pathways in the development of CRC, including the chromosomal instability (CIN) pathway, the DNA mismatch repair (MMR)/microsatellite instability (MSI) pathway, and the CpG island methylator phenotype (CIMP) pathway. The CIN pathway is the predominant pathway in the development of CRC in the general population, accounting for approximately 70-85% of CRCs. This pathway is characterized by gross chromosomal abnormalities that develop, including deletions, insertions, and loss of heterozygosity. The key gene that is altered early in the development of CRC is the adenomatous polyposis coli (APC) gene, a tumor suppressor protein. Pathogenic mutations lead to a loss of functional APC which has negative downstream consequences that result in cellular proliferation. The CIN pathway can also be associated with the loss of chromosome 5q, resulting in the loss of APC, a gain of function mutation in the KRAS oncogene, and/or eventual inactivation of the TP53 tumor suppressor gene. This pathway results in the transformation of adenomas to carcinoma, known as the adenoma-to-carcinoma sequence.

The MMR pathway involves MSI and represents approximately 15% of sporadic CRC diagnoses. Microsatellites represent nucleotide repeat sequences interspersed throughout the genome. The main genes implicated in the dysfunction of the MMR system are MLH1 and MSH2. MSI results when there is variation in the number of nucleotide repeats within microsatellite regions in germline versus tumor DNA due to defects by DNA polymerase when copying these sequences. CRC tumors are characterized by high levels of MSI. In addition to mutations in the MMR pathway, hypermethylation of gene sequences for the MMR enzyme can disrupt transcription of
the MMR enzyme gene expression.\textsuperscript{71} Epigenetic alterations including hypermethylation, can silence gene expression of the MMR enzymes.\textsuperscript{71,72}

This process of hypermethylation is what characterizes the CIMP pathway. Hypermethylation of the CpG islands (cytosine base linked to guanine base by a phosphodiester bond) occurs at a high frequency in CRC development, with subsequent hypermethylation of promoter genes of MMR enzymes (e.g., MLH1) resulting in impaired DNA mismatch repair mechanisms that foster cellular proliferation.\textsuperscript{71}

While there are commonalities in the CRC molecular pathways for patients within the general population and patients with IBD, there are specific IBD-related CRC (IBD-CRC) molecular pathways that are highlighted in the next section.

\textit{IBD-Colorectal Cancer Molecular Pathways}

Intestinal inflammation is an important risk factor for the development of CRC. Patients with more extensive and more severe disease are at a higher CRC risk. While the pathogenesis of CRC in IBD is not well understood, we know that a combination of genetic and environmental factors plays a role.\textsuperscript{73} The development of IBD-CRC is multifactorial, including genetic instability, epigenetic alteration, chronic inflammation, oxidative stress, and intestinal microbiota.\textsuperscript{73}

Similar to the development of sporadic CRC, defined as the formation of CRC in the absence of known genetic causes, significant family history of CRC or IBD, the development of IBD-CRC also involves the adenoma-to-carcinoma sequence.\textsuperscript{73} Whereas sporadic CRC often develops from one or two focal areas of dysplasia within the colon, IBD-CRC often develops from multifocal dysplasia, consistent with a “field change
The CIN and MSI pathways occur at similar frequencies in both sporadic CRC and IBD-CRC (roughly 85% and 15% respectively), but differ in the timing of when genetic instability occurs. Loss of APC function is projected to occur early on in sporadic CRC development, whereas it occurs later on in the development of IBD-CRC and with less frequency. Additionally, loss of TP53 is important in the development of IBD-CRC, and often occurs earlier on within nondysplastic tissue compared to sporadic CRC.

Lastly, the development of IBD-CRC also involves the CIMP pathway, with resultant silencing of key tumor suppressor genes, including DNA repair genes.

Chronic inflammation plays a key role in the pathogenesis of IBD-CRC, inducing changes in the microenvironment that confer an increased risk. Constant inflammation produces epithelial layer damage, resulting in chronic cellular proliferation to repair the damage; this in turn increases the risk for dysplasia formation. Inflammatory cytokines are thought to play a role in the pathogenesis of IBD-CRC, and are being researched in efforts to identify therapeutic targets.

Oxidative stress can develop in response to inflammatory reactions and contribute to the pathogenesis of IBD-CRC. The chronic activation of inflammatory cells, neutrophils, and macrophages can produce reactive oxygen and nitrogen species (RONs) in large quantities. RONs in turn can target key proteins and nucleic acids, leading to protein denaturation and altered DNA. It has been shown that inflamed tissues in patients with active IBD have increased expression of RONs, which can disrupt the function of critical genes within tumor development pathways, such as TP53 and DNA mismatch repair genes.
Intestinal microbiota also may contribute to CRC development in IBD, though the mechanism is not well understood and is currently being studied.76,77 Findings from studies of rodent models of IBD suggest that specific bacteria may contribute to the formation of colorectal dysplasia and neoplasia.73

Types of Dysplasia in IBD Patients

Dysplasia is defined as the “abnormal organization of cells within a specific tissue type.”82 From a macroscopic view, dysplasia in IBD can be categorized as polypoid, non-polypoid, or invisible.83 The histologic classification of dysplasia in IBD can be grouped into the following five categories: negative for dysplasia, indefinite for dysplasia, low-grade dysplasia (LGD), high-grade dysplasia (HGD), or invasive cancer.84 “Indefinite” for dysplasia encompasses diagnostic uncertainty in differentiating dysplasia from reactive epithelial changes.84 LGD and HGD are distinguished by the distribution of nuclei within cells (i.e., cellular polarity); LGD is associated with nuclei confined to the basal half of cells, whereas HGD involves nuclei distributed in a haphazard fashion between the basal and apical halves of cells.85 This distinction is predicated on the notion that the development of neoplasia from dysplasia is a result of progressive loss of cellular polarity.84 While patients may develop CRC without any prior dysplasia, CRC can arise from LGD and HGD.84 In some cases, LGD progresses to HGD before CRC arises, though not all cases progress in this fashion.86

Polypoid dysplasia is managed with endoscopic resection when possible. Polyps <2 cm without obvious features of invasive cancer or submucosal fibrosis and with clear delineation can be removed via endoscopic resection.87 Endoscopic removal of polyps >2
cm can be considered based on polyp characteristics, experience of the endoscopist, and disease activity. Simple lesions can be removed with standard en bloc resection techniques, while large and irregular appearing lesions may require advanced removal techniques, including endoscopic mucosal resection or endoscopic submucosal dissection.

Nonpolypoid dysplasia is managed via endoscopic removal when possible. These lesions can be technically challenging to remove, with some cases requiring endoscopists with experience performing advanced endoscopic resection.

Invisible dysplasia is identified from random (or “non-targeted”) biopsies of the colonic mucosa in the absence of an endoscopically visible lesion. The detection of unifocal and multifocal invisible LGD should be confirmed by a second pathologist with knowledge of IBD pathology, and followed up with high definition chromoendoscopy for better visualization of the area. For HGD detected in the absence of an endoscopically visible lesion, the European Crohn’s and Colitis Organization (ECCO) and the American Society for Gastrointestinal Endoscopy (ASGE) recommend surgical management.

In this next section, we detail screening and surveillance colonoscopy guidelines for patients with IBD as well as differences in surveillance intervals based on risk factors for dysplasia.

**Screening and Surveillance Colonoscopy in IBD**

The first colonoscopy exam to assess for colorectal neoplasia in someone who is average risk for colon cancer is referred to as the “screening colonoscopy.” Surveillance colonoscopy refers to evaluating patients with risk factors for CRC, including personal
history of adenomatous polyps, CRC in first-degree relative <60 at age of diagnosis, IBD, and hereditary CRC (e.g., familial adenomatous polyposis, hereditary nonpolyposis CRC).

For adults in the general population at average risk for developing CRC, colon cancer screening is recommended to start at age 45 in accordance with US Preventive Services Task Force (USPSTF) recommendations. While most cases of CRC occur over the age of 50, screening at 45 optimizes the benefits of CRC detection and prevention with the risks of potential harms from screening and patient burden. Screening until at least age 75 is recommended for average-risk patients based on the increased risk of CRC with age and time course progression from polyp to CRC.

In patients with IBD, the initial colonoscopy screening for dysplasia starts 8-10 years after onset of IBD symptoms, with evidence that the risk of CRC begins around 7 years after diagnosis and steadily increases thereafter. Diagnosis of IBD at a young age, longer duration of disease, and severe colonic inflammation are all associated with increased risk of CRC. Family history of CRC in patients with IBD confers a two-to-three-fold risk of developing CRC, and diagnosis of PSC should prompt immediate CRC screening since we know that subclinical colitis may be present in these patients for years prior to diagnosis.

Initial screening colonoscopy examinations involve staging biopsies to evaluate the disease extent (based on histologic changes suggestive of current or previously active inflammation) and to determine the appropriate surveillance intervals based on the colonoscopy findings. Screening guidelines for patients with IBD recommend a high-quality colonoscopy in efforts to optimize dysplasia and neoplasia detection. This entails
conducting the colonoscopy when patients are in clinical remission (i.e., disease is well-controlled), given that ongoing inflammation can mask subtle precancerous findings and detection of inflammation can be misinterpreted as dysplasia.\textsuperscript{100} In addition, excellent bowel preparation, use of high-definition endoscopy, adequate insufflation, careful washing and inspection of colorectal mucosa, and targeted sampling of visual mucosal irregularities are essential to optimize dysplasia detection.\textsuperscript{87,101,102}

After initial screening colonoscopy has been performed, guidelines recommend that patients with IBD undergo routine surveillance colonoscopy. There is a consensus that patients with IBD and comorbid PSC should undergo annual surveillance.\textsuperscript{93} Patients with IBD without comorbid PSC are recommended to undergo surveillance colonoscopy, and intervals vary based on the status of clinical remission, familial CRC risk factors, the presence or absence of dysplasia, whether dysplasia is visible or invisible, and grading of the dysplasia. The recommendations of multiple society guidelines are summarized in Table 1.
**Table 1: Surveillance Colonoscopy Guidelines for Patients with IBD**

<table>
<thead>
<tr>
<th>Society</th>
<th>Screening initiation, after symptom onset</th>
<th>Surveillance Intervals</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACG 2019 (UC Only)(^50)</td>
<td>8-10 years</td>
<td><strong>Every 1-3 years</strong></td>
<td>PSC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>UC extending beyond rectum</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjust intervals based on disease extent and duration, family history of CRC in first degree relative, and age at diagnosis</td>
<td></td>
</tr>
<tr>
<td>AGA 2021(^87)</td>
<td>8-10 years</td>
<td><strong>Every 5 years</strong></td>
<td>PSC, Family history of CRC in first degree relatives younger than 50 years, personal history of invisible dysplasia or high-risk visible dysplasia within 5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Every 2-3 years</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild inflammation of any extent, Family history of CRC in first degree relative &gt;50 years, severe colitis features (i.e., pseudopolyposis,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ASGE 2015&lt;sup&gt;103&lt;/sup&gt;</td>
<td>8 years</td>
<td>Every 3+ years</td>
</tr>
<tr>
<td>------</td>
<td>-------------------------</td>
<td>---------</td>
<td>----------------</td>
</tr>
<tr>
<td></td>
<td>exam, plus 2 or more surveillance colonoscopy with normal endoscopic and histologic findings</td>
<td>mucosal scarring, history of visible low grade dysplasia within 5 years, history of invisible dysplasia or visible high grade dysplasia more than 5 years ago, years, dense pseudopolyps, moderate to severe inflammation of any extent</td>
<td>2 or more surveillance colonoscopy with normal endoscopic and histologic findings</td>
</tr>
<tr>
<td>ECCO 2017 (UC only)(^{104})</td>
<td>8 years</td>
<td><strong>Low risk (every 5 years)</strong></td>
<td><strong>Intermediate risk (every 2-3 years)</strong></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Not intermediate or high risk</td>
<td>History of CRC in first degree relative older than 50 years, presence of pseudopolyps, mild-moderate inflammation in the setting of extensive colitis</td>
<td></td>
<td>History of CRC in first degree relatives younger than 50 years, severe active inflammation in setting of extensive colitis, stricture or dysplasia found within past 5 years</td>
</tr>
</tbody>
</table>

*ASGE = American Society for Gastrointestinal Endoscopy, ECCO = European Crohn’s and Colitis Organisation, ACG = American College of Gastroenterology, AGA = American Gastroenterological Association*
All societies recommend more frequent surveillance colonoscopy in patients with IBD involving at least one-third of the colon or more than one colon segment.\(^93\) Methods for surveillance include chromoendoscopy with targeted biopsies (random biopsies may also be taken) and high definition (HD) white light endoscopy (WLE) with random and targeted biopsies. WLE includes standard definition (SD) and HD, with HD WLE resulting in better image detail and improved display of moving objects.\(^93,105\)

Chromoendoscopy is a newer technique that applies blue contrast dye of indigo or methylene blue to the colonic mucosa to better visualize irregular areas and borders of suspicious lesions.\(^93\) Most society guidelines recommend HD endoscopy with surface chromoendoscopy for optimal dysplasia detection.\(^91,103,106\) Society guidelines recommend the use of HD WLE with random and targeted biopsies in cases where chromoendoscopy yield is reduced and/or the mucosa is poorly visualized.\(^91,103,106\)

Recent studies have found that dye chromoendoscopy with targeted biopsies was no better than HD WLE with random biopsies in detecting colitis-associated dysplasia for patients with UC.\(^107\) Virtual chromoendoscopy is a newer technology being investigated as an alternative to dye chromoendoscopy, and has promise in conjunction with narrow band imaging (NBI) for detection of dysplastic lesions.\(^93\)

**Quality Indicators of Colonoscopy**

In efforts to maximize the effectiveness of the colonoscopy evaluation, several quality indicators have been developed to ensure competency in performing high quality colonoscopy.\(^108\) The ASGE and the U.S. Multi-Society Task Force on Colon Cancer have published specific quality indicators for colonoscopy.\(^90\) Quality evaluation of the colon
involves intubation of the entire colon and a thorough inspection of the colonic mucosa. The main evidence-based quality indicators for colonoscopy include adequacy of bowel preparation, the endoscopist’s cecal intubation rate, the endoscopist’s adenoma detection rate (ADR), and the average colonoscopy withdrawal time (CWT) for negative exams.

Quality bowel preparation is essential for a quality colonoscopy evaluation. Some endoscopists characterize bowel preparation using subjective terms such as “excellent,” “good,” “fair,” or “poor;” excellent refers to minimal solid stool as well as minimal clear fluid requiring suctioning, whereas poor is characterized by solid or semisolid stool that cannot be cleared effectively. Others rate the adequacy of bowel preparation using a validated instrument called the Boston Bowel Preparation Scale (BBPS), a nine-point scale that assesses bowel preparation after cleansing maneuvers have been attempted. The BBPS assigns a score of zero to three points to each colon segment (i.e., right colon, transverse colon, left colon) based on the presence of stool and the ability to adequately visualize the mucosa. A score of nine correlates with a perfectly clean colon without residual liquid, while a score of zero implies that all segments of the colon cannot be adequately visualized. A poor bowel preparation is a sign of a poor quality colonoscopy, linked to reduced detection of small and large polyps. Guidelines recommend a repeat colonoscopy within one year in the setting of a poor bowel preparation, which contributes to substantial healthcare costs.

Cecal intubation, defined as the passage of the colonoscope tip to a point proximal to the ileocecal valve so that the cecum may be visualized, is an important part of the colonoscopy. Cecal intubation is documented with identification of key landmark
structures, including the ileocecal valve and appendiceal orifice. Photo documentation is also recommended for confirmation. It is recommended that endoscopists intubate the cecum in \( \geq 90\% \) of total cases and \( \geq 95\% \) of cases involving screening of a healthy adult.\textsuperscript{113,114} Low cecal intubation rates have been linked to an increased risk of interval CRC.\textsuperscript{115}

ADR is the most established quality indicator for colonoscopy.\textsuperscript{109} ADR is defined as the proportion of screening colonoscopies with at least one adenoma detected. It is calculated for each endoscopist by taking the number of screening colonoscopies with at least one adenoma detected, and dividing it by the total number of screening colonoscopies performed.\textsuperscript{109} It is recommended that for healthy, asymptomatic patients requiring screening colonoscopy, adenomas should be detected in \( \geq 25\% \) of men and \( \geq 15\% \) women over 50 years of age.\textsuperscript{108} A landmark study in Poland found that endoscopists with an ADR < 20\% for screening colonoscopy had a 10-fold higher incidence of interval CRCs compared to endoscopists with an ADR \( \geq 20\% \).\textsuperscript{116} Additionally, a study done in the US illustrated that a 1\% increase in ADR correlates with a 3\% risk reduction of interval CRCs and 5\% risk reduction of fatal interval CRCs.\textsuperscript{117} It is thought that a portion of interval CRCs that develop in these scenarios may be attributed to missed lesions during colonoscopy.

CWT is another important quality indicator, with several studies showing that withdrawal time positively correlates with ADR and thus may serve as a proxy for ADR and reflect cancer risk after screening.\textsuperscript{118} CWT is defined as time from intubation of the cecum to withdrawal of the colonoscope from the anus. In 2002, the ASGE/American College of Gastroenterology (ACG) Task Force on Quality in Endoscopy recommended a
CWT of at least six minutes as an indicator of a quality colonoscopy. A landmark study by Barclay and colleagues in 2006 also found that a CWT greater than six minutes is associated with an increased ADR. Several studies since then have demonstrated that longer CWT is associated with improved rates of adenoma and polyp detection, with the majority deducing that a CWT between eight and ten minutes is optimal. Additionally, the relationship between increasing mean CWTs and cancer detection is unclear, with several studies reporting no significant association between CWT rates of cancer detection, while others have determined that detection of advanced neoplasia is significantly higher with longer mean CWT.

The association of CWT in patients with IBD undergoing surveillance colonoscopies and polypoid dysplasia detection has not been fully evaluated. In fact, many pivotal studies that investigated the significance of CWT in the general population have excluded patients with IBD. Given the increased risk of CRC and CRC-related mortality in patients with IBD, prompting routine surveillance colonoscopy, further study of CWT and its significance is warranted in this population.

**Statement of Purpose**

Our study aims to evaluate the relationship between CWT and polypoid dysplasia detection in patients with IBD undergoing surveillance with high-definition white light colonoscopy. We also aim to define a cutoff CWT associated with a high sensitivity and specificity for the detection of polypoid dysplasia in patients with IBD.
Materials and Methods

Student Contributions

Chandler McMillan and Dr. Badr Al Bawardy were responsible for the study conception, design, and thesis drafting. The majority of the thesis writing was completed by Chandler McMillan. Dr. Jill Gaidos and Dr. Deborah Proctor also contributed to the study design. Dr. Darrick Li was responsible for identifying eligible patients with IBD undergoing colonoscopy at Yale from Provation® Medical using study inclusion criteria, and Chandler McMillan was solely responsible for the data collection. Gamal Mohamed, Danah A. Alsadoun, and Leena A. Almohsen were responsible for the statistical analysis and data presentation. All team members contributed to thesis revisions.

Ethics Statement

This study was approved for medical record review only, and patient privacy and confidentiality was maintained when extracting data from charts in Epic in accordance with the Yale University Institutional Review Board guidelines. Chandler McMillan received funding for this study from the Richard Alan Hirschfield Memorial Fellowship and the Taylor Opportunity Student Research Fellowship Fund through the Yale School of Medicine Office of Student Research. She has no conflict of interests. Financial disclosures and conflicts of interest for the other authors are reported below:

- Dr. Jill K. J. Gaidos: Advisory Board: Bristol-Myers Squibb, Pfizer, Takeda; Consulting: MRM Health
• Dr. Deborah D. Proctor, AbbVie consulting
• All other authors have no financial disclosures.

**Human Subject Research**

The study protocol was approved by the Yale University Institutional Review Board (IRB#2000033392). Given that this retrospective chart review deidentified patient information from collected data, the study was granted an exemption and full waiver of HIPAA Authorization.

**Methods Description**

This was a single-center, retrospective review of all patients with IBD in endoscopic remission undergoing surveillance via high-definition white light colonoscopy from 6/1/2017 – 9/1/2022.

**Patient Characteristics:**

We included subjects at least 18 years of age who had a confirmed diagnosis of CD, UC and IBD-unclassified involving the colon for ≥ eight years, or a confirmed diagnosis of IBD and PSC. We excluded subjects with the following criteria: active inflammation (defined as the presence of erosions and/or ulcers in CD, and an MES > 1 in UC), and poor bowel preparation [defined as a BBPS less than six or bowel preparation categorized as “poor” by the performing endoscopist]. We also excluded subjects who underwent standard definition colonoscopy, dye-chromoendoscopy,
subjects with incomplete colonoscopy (defined as colonoscopies that failed to intubate the cecum), and subjects with prior ileocolonic and/or colonic resections.

Variables Collected:

Baseline characteristics and disease-related variables were extracted from patient charts including age, sex, race and ethnicity, body mass index (BMI), smoking status, personal history of invisible dysplasia and polypoid dysplasia, family history of CRC, IBD disease duration, subtype, location, phenotype, current and previous IBD therapies.

Additional variables extracted from the patient colonoscopy reports included credentials of the performing endoscopist (gastroenterology fellow, attending, IBD specialist), presence of pseudopolyps, presence of colonic strictures, number of polyps identified, and whether random biopsies were obtained. Pathology reports from each colonoscopy were reviewed to determine the presence of invisible and/or polypoid dysplasia. Invisible dysplasia was defined as the absence of an endoscopically visible lesion with pathology supporting indefinite, low, or high-grade dysplasia. Polypoid dysplasia was defined as the presence of an endoscopically visible lesion with pathology showing indefinite, low, or high-grade dysplasia, adenoma, or sessile serrated polyp (SSP). CWT was defined as the time from cecal intubation to withdrawal of the colonoscope from the anal canal, rounded to the nearest whole minute.
Outcomes:

The primary outcome was to evaluate the association between CWT and the presence of polypoid dysplasia. The secondary outcome was to identify an optimal CWT cutoff associated with polypoid dysplasia detection.

Statistical Analysis:

All statistical analyses were performed using Stata version 17. For variables that were normally distributed, the data was summarized as mean and standard deviations. Variables that were not normally distributed were summarized as medians with interquartile ranges. CWT cut-off values were tested for association with polypoid dysplasia detection. A CWT of nine minutes was initially chosen as recent evidence has suggested that it is superior to a six-minute withdrawal time in the general population.\textsuperscript{126} CWT was then divided into three groups using cut-off times of 9 minutes, 15 minutes, and 20 minutes. CWT, mean number of polypectomies and patient characteristics were compared based on whether polypoid dysplasia was present or not. Unpaired t-tests were employed to compare continuous variables, whereas Pearson’s Chi square test was used to compare categorical variables. Multivariable logistic regression analysis was performed to assess the joint association of patient characteristics with polypoid dysplasia. Results from logistic regression were presented as odds ratio with 95% confidence interval. Receiver operating characteristic curve (ROC) was used to determine the optimal cut-off point of CWT for detecting polypoid dysplasia detection. The area under the ROC curve (AUC) with its 95% confidence interval was used to assess the predictive ability of CWT to detect polypoid dysplasia. Based on the cut-off point
determined by the ROC curve and selected cut-off points for CWT (6, 9, 15, 20, and 25 minutes), the sensitivity and specificity of CWT to detect polypoid dysplasia were computed. A p-value < 0.05 was considered statistically significant.

**Results**

A total of 259 subjects underwent 330 colonoscopies and were included in the study. The mean age was 56 ± 14.8 years and 51.3% of subjects were female. Regarding IBD subtype, 30.9% of subjects had CD, 68% had UC, and 1.1% had IBD-unclassified. The median disease duration of IBD in the cohort was 15 years [interquartile range (IQR) 8-24]. A total of 23 (8.9%) subjects had a diagnosis of PSC, and 15 (5.8%) subjects were active smokers at the time of colonoscopy. A previous history of polypoid dysplasia was noted in 64 (24.7%) and 12 (4.6%) subjects had a personal history of invisible dysplasia (Table 2). IBD specialists performed 135 (40.9%) colonoscopies, and 32 (9.7%) of colonoscopies were performed by supervised gastroenterology fellows. Random biopsies were obtained in 321 (97.3%) of colonoscopies performed. The median CWT for the cohort was 22 minutes (IQR 15-29).

**Table 2: Baseline Characteristics of Subjects with IBD Included in the Study**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>56.0 (14.8)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>133 (51.3)</td>
</tr>
<tr>
<td>BMI, median (IQR)</td>
<td>27.4 (24-31.8)</td>
</tr>
<tr>
<td>Disease duration (years), median (IQR)</td>
<td>15 (8-24)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>Caucasian</td>
<td>205 (79.2)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>18 (6.9)</td>
</tr>
<tr>
<td>African American</td>
<td>25 (9.7)</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>Others</td>
<td>6 (2.3)</td>
</tr>
<tr>
<td>Multi-racial</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IBD subtype</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s disease, n (%)</td>
<td>80 (30.9)</td>
</tr>
<tr>
<td></td>
<td>L2 40</td>
</tr>
<tr>
<td></td>
<td>L3 40</td>
</tr>
<tr>
<td></td>
<td>B1 48</td>
</tr>
<tr>
<td></td>
<td>B2 13</td>
</tr>
<tr>
<td></td>
<td>B3 19</td>
</tr>
<tr>
<td>Ulcerative colitis, n (%)</td>
<td>176 (68.0)</td>
</tr>
<tr>
<td></td>
<td>Proctitis 15</td>
</tr>
<tr>
<td></td>
<td>Left-sided colitis 63</td>
</tr>
<tr>
<td></td>
<td>Pancolitis 95</td>
</tr>
<tr>
<td>IBD-unclassified, n (%)</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis, n (%)</td>
<td>23 (8.9)</td>
</tr>
<tr>
<td>Personal history of polypoid dysplasia, n (%)</td>
<td>64 (24.7)</td>
</tr>
<tr>
<td>Personal history of invisible dysplasia, n (%)</td>
<td>12 (4.6)</td>
</tr>
<tr>
<td>Family history of colorectal cancer, n (%)</td>
<td>26 (10.0)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>15 (5.8)</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td>Oral mesalamine, n (%)</td>
<td>125 (48.3)</td>
</tr>
<tr>
<td>On biologic, n (%)</td>
<td>69 (26.7)</td>
</tr>
<tr>
<td>Infliximab, n</td>
<td>34</td>
</tr>
<tr>
<td>Adalimumab, n</td>
<td>14</td>
</tr>
<tr>
<td>Vedolizumab, n</td>
<td>14</td>
</tr>
<tr>
<td>Ustekinumab, n</td>
<td>6</td>
</tr>
<tr>
<td>Certolizumab pegol, n</td>
<td>1</td>
</tr>
<tr>
<td>Tofacitinib, n (%)</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>On Immunomodulator</td>
<td>47 (18.1)</td>
</tr>
<tr>
<td>Thiopurine</td>
<td>42</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>5</td>
</tr>
</tbody>
</table>

*IBD: inflammatory bowel disease; SD: standard deviation; IQR: interquartile range*

**Dysplasia Detection**

Invisible dysplasia was detected in 2.1% (n=7); of these seven colonoscopies, one also had polypoid dysplasia. The overall rate of polypoid dysplasia detection in the sample was 17.3% (n=57). This represents the proportion of colonoscopies that detected at least one type of polypoid dysplasia. Adenomas were detected in 43 of the procedures while SSPs were detected in 16 procedures (two procedures had both adenoma and SSPs detected). A total of 60 adenomas and 19 SSPs were detected in these colonoscopies. Of the 60 adenomas, one was noted to be polypoid HGD, one was tubulovillous adenoma,
12 were tubular adenomas, and 46 were polypoid LGD. Differences in baseline and disease characteristics between the groups with and without polypoid dysplasia detection are shown in Table 3.

**Table 3: Comparison of Characteristics between Subjects with and without Polypoid Dysplasia**

<table>
<thead>
<tr>
<th></th>
<th>Polypoid dysplasia (n=45 subjects)</th>
<th>No polypoid dysplasia (n=214 subjects)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>62.9 (12.5)</td>
<td>54.6 (14.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex, n (%),</td>
<td>25 (55.6)</td>
<td>101 (47.2)</td>
<td>0.31</td>
</tr>
<tr>
<td>Smoking, n (%),</td>
<td>3 (6.7)</td>
<td>11 (5.1)</td>
<td>0.68</td>
</tr>
<tr>
<td>Family history of CRC, n (%)</td>
<td>4 (8.9)</td>
<td>23 (10.8)</td>
<td>0.71</td>
</tr>
<tr>
<td>Disease duration (years), median (IQR)</td>
<td>14 (8-24)</td>
<td>15 (8-24)</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Disease characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease type, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>12 (26.7)</td>
<td>68 (31.8)</td>
<td>0.56</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>33 (73.3)</td>
<td>143 (66.8)</td>
<td></td>
</tr>
<tr>
<td>Indeterminate colitis</td>
<td>0 (0)</td>
<td>3 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Primary sclerosing cholangitis, n (%)</td>
<td>2 (4.4)</td>
<td>20 (9.4)</td>
<td>0.28</td>
</tr>
</tbody>
</table>
Compared to subjects without polypoid dysplasia, subjects with polypoid dysplasia were older (62.9 years vs 54.6 years, p<0.001) and more likely to have a personal history of polypoid dysplasia (p<0.001) or invisible dysplasia (p=0.023). There were no significant differences between the two groups when we assessed for gender, smoking history, family history of CRC or disease duration (Table 3). There were also no significant differences between the groups when assessing for procedural factors, such as bowel preparation, presence of pseudopolyps and colonic stricture, as well as

| Personal history of polypoid dysplasia, n (%) | 21(46.7) | 43(20.1) | <0.001 |
| Personal history of invisible dysplasia, n (%) | 5 (11.1) | 7 (3.3) | 0.02 |

**Medications**

| On mesalamine at time of colonoscopy, n (%) | 19 (42.2) | 103 (48.1) | 0.47 |
| On biologic at time of colonoscopy, n (%) | 10 (22.2) | 62 (28.9) | 0.36 |
| Steroids at time of colonoscopy, n (%) | 3 (6.7) | 11 (5.1) | 0.68 |
| On tofacitinib, n (%) | 1 (2.2) | 3 (1.4) | 0.69 |
| On immunomodulator, n (%) | 5 (11.1) | 40 (18.7) | 0.22 |

SD: standard deviation; CRC: colorectal cancer; IQR: interquartile range; IBD: inflammatory bowel disease

**Bold indicates p-value < 0.05**
proceduralist factors including the presence of an IBD specialist or gastroenterology fellow (Table 4).

Table 4: Comparison of Procedural Factors Among Colonoscopies With and Without Polypoid Dysplasia Detection

<table>
<thead>
<tr>
<th>Procedure Factors</th>
<th>Polypoid dysplasia (n=57 colonoscopies)</th>
<th>No polypoid dysplasia (n=273 colonoscopies)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent/good bowel preparation, n (%)</td>
<td>49 (85.9)</td>
<td>251 (91.9)</td>
<td>0.15</td>
</tr>
<tr>
<td>Withdrawal time, median (IQR)</td>
<td>26 (20-38)</td>
<td>21 (15-28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pseudopolyps, n (%)</td>
<td>10 (17.5)</td>
<td>41 (15.0)</td>
<td>0.63</td>
</tr>
<tr>
<td>Colonic stricture, n (%)</td>
<td>1 (1.8)</td>
<td>5 (1.8)</td>
<td>0.97</td>
</tr>
<tr>
<td>Proceduralist Factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD specialist, n (%)</td>
<td>20 (35.1)</td>
<td>115 (42.1)</td>
<td>0.33</td>
</tr>
</tbody>
</table>
Colonoscopy Withdrawal Time

The CWT was significantly higher in the polypoid dysplasia group at 26 minutes (IQR 20-38.5) compared to a median CWT of 21 minutes (IQR 15-28) for colonoscopies that did not detect polypoid dysplasia (p<0.001) (Figure 1). At least one polypectomy was performed in 74 colonoscopies in the group without polypoid dysplasia where pathology was consistent with hyperplastic polyps. The mean number of polypectomies was 2.1 ± 1.5 in this group of colonoscopies (n=74) and 2.3 ± 2.3 in the group with polypoid dysplasia (n=57) (p=0.71).

**Figure 1**: Box plot comparing colonoscopy withdrawal time in the group with and without polypoid dysplasia.
Variables Associated with Polypoid Dysplasia Detection

On multivariable analysis, increasing age (OR 1.04, 95% CI: 1.02-1.07, p<0.001), longer CWT (OR 1.04; 95% CI: 1.02-1.06, p=0.001), and personal history of polypoid dysplasia (OR 2.24; 95% CI: 1.18-4.25, p=0.013) were all independently associated with an increased odds of polypoid dysplasia detection (Table 5). CWT cutoffs of ≥15 minutes (OR 2.71; 95%CI: 1.11-6.60, p=0.02) and ≥20 minutes (OR 3.02; 95% CI: 1.53-5.98, p<0.001) were significantly associated with the detection of polypoid dysplasia. Conversely, a CWT cutoff of ≥9 minutes (OR 2.57; 95% CI: 0.33-20.2, p=0.35) was not significantly associated with the detection of polypoid dysplasia. Assessing CWT as a continuous variable, we found that for every 1-minute increase in CWT, there was a subsequent 4.2% increase in polypoid dysplasia detection (OR 1.04; 95% CI, 1.02 – 1.06, p=0.001). A receiver operating characteristics (ROC) curve demonstrated an area under the curve (AUC) of 0.65 (95% CI: 0.57 – 0.73) for a CWT cutoff of 23 minutes (Figure 2).

Table 5: Multivariable Regression Analysis of Factors Associated with Polypoid Dysplasia

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratios</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.04</td>
<td>1.02-1.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>0.98</td>
<td>0.96-1.00</td>
<td>0.11</td>
</tr>
<tr>
<td>Withdrawal time (minutes)</td>
<td>1.04</td>
<td>1.02-1.06</td>
<td>0.001</td>
</tr>
<tr>
<td>Personal history of polypoid dysplasia</td>
<td>2.24</td>
<td>1.18-4.25</td>
<td>0.013</td>
</tr>
</tbody>
</table>
Discussion

In this study, we evaluated the relationship between patient and procedural variables, including CWT, and polypoid dysplasia detection in subjects with IBD. The overall rate of polypoid dysplasia detection in our cohort was 17.3%, and multivariable analyses demonstrated that longer CWT is independently associated with polypoid dysplasia detection in subjects with IBD. Specifically, a CWT cutoff $\geq 15$ minutes was significantly associated with polypoid dysplasia detection in this group of subjects with IBD.
IBD. Conversely, a CWT cutoff $\geq$ 9 minutes was not significantly associated with polypoid dysplasia detection. When evaluating CWT as a continuous variable, we found that there was a subsequent 4.2% increase in polypoid dysplasia detection for every 1-minute increase in CWT. The mean CWT was significantly longer in the polypoid dysplasia group at 26 minutes vs. 21 minutes in procedures without polypoid dysplasia. Lastly, compared to subjects without polypoid dysplasia, subjects with polypoid dysplasia were more likely to be older and have a personal history of polypoid dysplasia and/or invisible dysplasia.

In the general population, multiple society guidelines and consensus statements have recommended a minimum CWT of at least 6 minutes. The landmark study conducted by Barclay et al. in 2006 evaluated CWT and ADR for 12 endoscopists and determined that endoscopists with a mean CWT $\geq$ 6 minutes had significantly higher rates of adenoma, advanced adenoma, and neoplasia detection compared to endoscopists with a mean CWT < 6 minutes. More recent prospective studies in the general population have proposed a longer CWT cutoff of 9 minutes for optimal detection of adenomas and polyps. These studies have excluded patients with IBD and hence it is unclear if this ideal CWT cutoff time is applicable to patients with IBD.

Recent studies have demonstrated a reduction in the rate of CRC incidence in IBD, likely owing to improvement in medical management and CRC surveillance. However, the relative risk of developing CRC in UC and colonic CD is two-fold higher compared to the general population. In addition, the burden of CRC in IBD is not trivial as it is responsible for 10%-15% of the annual mortality in patients with IBD. Patients with IBD are also prone to developing dysplasia in both endoscopically visible
and invisible lesions, and the presence of low-grade dysplasia in this population confers a nine-fold increase in risk of neoplasia development compared to a 1.8-fold risk of neoplasia in the general population.\textsuperscript{135,136,106,107} Given the increased risk for transformation of low-grade dysplasia to neoplasia in patients with IBD, surveillance colonoscopy requires meticulous inspection of the mucosa, and identification and removal of dysplastic lesions when possible. Thus, patients with IBD may require longer average CWTs compared to average risk patients undergoing screening colonoscopy.

In our cohort, the rates of invisible and polypoid dysplasia were 2.1% and 17.3%. This is similar to previous reports including a population-based study which showed a prevalence of neoplasia associated with UC to be 23.6% (this included adenomas and CRC).\textsuperscript{137} Risk factors for colonic dysplasia associated with IBD include disease duration, extent, cumulative inflammation, smoking, age, family history and PSC.\textsuperscript{138,139} The patient population included in our study were at a relatively higher risk for colonic neoplasia with a mean age of 56 years, median disease duration of 15 years and almost 9% with concomitant PSC. We did not have any cases of colon cancer in our cohort and that is likely due to patient selection per pre-determined criteria. We did not include all consecutive subjects with IBD undergoing surveillance colonoscopy as we excluded subjects who had active inflammation or suboptimal bowel preparation.

Our study focuses on CWT and polypoid dysplasia detection in patients with IBD specifically as this population is at higher risk of CRC compared to the general population and there are no guidelines that define the optimal CWT for CRC surveillance in this cohort of patients. There are no previous studies looking at the relationship between CWT and dysplasia detection in IBD. A recent systematic review of quality
metrics in IBD surveillance colonoscopies suggested at least a 17-minute withdrawal time when performing dye chromoendoscopy.\textsuperscript{140} This was based on an average of an additional 11 minutes needed during withdrawal of dye chromoendoscopy exams which would be dedicated to washing the mucosa, applying the dye, careful inspection of the mucosa and suction of fluid.\textsuperscript{141} However, no clear consensus or recommendation was made to the ideal minimum withdrawal time for high-definition white light colonoscopy surveillance exams in patients with IBD. Therefore, our findings offer new insight regarding this important quality indicator and predictor of adenoma detection. We have found that a minimum CWT of at least 15 minutes but not 9 minutes is associated with increased polypoid dysplasia detection. We were also able to demonstrate that CWT is an independent predictor of polypoid dysplasia detection.

There are multiple strengths to our study. We have included a homogenous population of subjects by selecting those in endoscopic remission and adequate bowel preparation to limit confounders of CWT. We also have a relatively high number of colonoscopies included in the study (> 300). Our study is the first to examine the relationship of CWT during high-definition white light colonoscopy surveillance exams in patients with IBD.

**Challenges and Limitations**

Our study also has several limitations. For one, this is a single-center retrospective study, therefore, we are unable to control for the withdrawal technique of each endoscopist which may ultimately impact reported withdrawal times. Secondly, we are not able to account for time taken to perform biopsies or polypectomies. However, our
study included 74 colonoscopies in the non-dysplasia group in which polypectomies were performed compared to the 57 in the dysplasia group with a similar median number of polypectomies of two per each colonoscopy in both groups. In addition, it is possible that clinicians may perform a more thorough withdrawal examination on colonoscopy when cognizant of a patient’s prior history of visible and/or invisible dysplasia, which could potentially contribute to a higher dysplasia detection rate. Another limitation is that we are unable to differentiate age-related sporadic adenoma from inflammation-related dysplasia. Lastly, our cohort reflects that of a tertiary referral center who were at a relatively higher risk of dysplasia and hence results might not be generalizable.

In conclusion, our study found that CWT was independently associated with polypoid dysplasia detection in IBD surveillance exams. Mean CWT was significantly longer in patients with polypoid dysplasia compared to patients without polypoid dysplasia detected, and the mean number of polypectomies were not significantly different between the two groups. Patients who were older in age, had a personal history of polypoid dysplasia, or a personal history of invisible dysplasia were more likely to have polypoid dysplasia detected on colonoscopy. Specifically, a CWT cutoff of ≥15 minutes was significantly associated with polypoid dysplasia detection, while a CWT of ≥ 9 minutes was not. Every 1-minute increase in withdrawal time was associated with a 4.2% increase in polypoid dysplasia detection. Future directions include prospective controlled studies to better ascertain the relationship between CWT and polypoid dysplasia detection in patients with IBD.
Dissemination

Several efforts have been made to distribute the findings from this study with the scientific community at large. An abstract for this study was submitted to the 2023 Digestive Disease Week (DDW) Annual Meeting in Chicago, IL, and was accepted for an oral presentation. The study was also presented locally at The Anlyan Center for the 2023 Yale School of Medicine Student Research Day. Additionally, the study team has submitted a manuscript summarizing the research findings for publication.

References


64. Alipour Z, Stashek K. Recently described types of dysplasia associated with IBD: tips and clues for the practising pathologist. J Clin Pathol [Internet] 2023;Available from: http://dx.doi.org/10.1136/jcp-2023-209141


