INCREASED MORTALITY IN YOUNGER PATIENTS WITH INFLAMMATORY BOWEL DISEASE ASSOCIATED COLORECTAL CANCER: A POPULATION-BASED COHORT STUDY

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Introduction and Literature Review

a. Defining Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a chronic autoimmune disease of the intestine that is comprised of two main subtypes: Crohn's disease and ulcerative colitis. The exact etiology of these diseases is unknown; but there is thought to be an environmental component related to the intestinal microbiome as well as a genetic predisposition as there is a hereditary pattern to the disease. Multiple genetic alterations have been identified in relation to the development of IBD, some are common to both Crohn's and ulcerative colitis, while others are unique to one of the subtypes.[1] IBD is commonly diagnosed in young adulthood, with peak onset of disease between 20-29 years of age, although the diagnosis can be made anywhere from in early childhood to elder years.[2]

Crohn's Disease is a condition that can impact the entire gastrointestinal tract, from the mouth to the anus. It is predominantly found in the terminal ileum, the last section of the small intestine, but can commonly manifest with colonic and perianal disease. Crohn's is considered a trans-mural disease, meaning that it involves the entire thickness of the bowel wall. It can lead to fistulas, bowel perforation and abscesses. The presence of Crohn's disease can have "skip lesions" meaning that the disease is not continuous and can be involving multiple separate areas of the gastrointestinal tract.[1] Treatment is multimodal, with the use of anti-inflammatory medications, antibiotics, surgery and immune modulating medications. In Crohn's disease, surgery is used to treat complications and significant symptoms, but will not be curative of the disease.

Ulcerative colitis is an inflammatory disease which is limited to the colon and rectum. It begins in the rectum and travels proximally, involving part of or the entire colon. When the entire colon and rectum is involved, it is termed pancolitis. Unlike Crohn's disease, there are no "skip lesions" and the segments of the colon that are impacted are continuous. It is a disease that does not involve the entire thickness of the bowel wall, but is limited to the mucosal layer.[1] The severity of colitis is variable and the requirement of medical therapy depends on the degree of inflammation and the patient's symptoms. Medical treatment is similar to that of Crohn's disease including steroids, anti-inflammatory medications, and drugs targeting the immune system. Ultimately, patients who have severe colitis may require surgical treatment with colectomy, or removal of the colon and rectum. Unlike in Crohn's disease, surgical removal of the entire colon and rectum can be curative.[3]

Both Crohn's and ulcerative colitis also have extra-intestinal manifestations that can affect patients. These include but are not limited to: primary sclerosing cholangitis (PSC), uveitis, psoriasis and ankylosing spondylitis.[1] The behaviour of these extra-intestinal manifestations may be impacted or worsened by active inflammation or "flares" of the IBD. While some improve with treatment of the bowel disease, others persist despite treatment of the bowel inflammation.

There are several families of medical therapy that are used to treat IBD. They include anti-inflammatory agents, antibiotics, corticosteroids, and immune targeted agents.[4,5] Medications such as steroids and antibiotics are often used in times of acute change, whereas immune targeted agents often act as maintenance therapy to control active disease and to prevent recurrent flares.

Within Ontario, Canada one of the most populous provinces, the incidence of IBD is 21.6 (95% CI, 21.4–21.9) per 100,000 person years and the prevalence is 1 in 200 people. The diagnosis of Crohn's disease occurs in 47.6% of patients, ulcerative colitis is diagnosed in 48.3% and 4.1% have IBD that cannot be classified as either subtype.[6]

b. Epidemiology of colorectal cancer

Colorectal caner (CRC) is the second most common cancer in Canada.[7] Although incidence overall is decreasing, the incidence of colorectal cancer in young adults (diagnosed under 50 years old) is increasing.[8,9] Colorectal Cancer is staged according to the American Joint Committee on Cancer (AJCC) Tumor-Node-Metastasis (TNM) system.[10] The depth of tumor invasion in the bowel wall determines the Tumor (T) status. The presence and number of lymph node metastases determines the nodal (N) status, and spread beyond the regional lymph nodes, is considered metastatic (M). Stage I and II disease are limited to the bowel and have not spread to regional nodes, whereas Stage III disease involves the bowel and the regional nodes. Colon cancer that has metastasized (M1) is Stage IV disease.[11]

Approximately 50% of patients present with Stage I and Stage II disease (24% Stage I, 24% Stage II), 29% present as Stage III disease and 20% present as Stage IV disease.[7,12] Five-year survival for patients of all stages in the province of Ontario is 67%.[7] Surveillance Epidemiology and End Results (SEER) data shows stage specific survival in the United States. Five-year survival in Stage

I and II patients is 91.1%; it is 71.7% in Stage III patients and is 13.3% in patients with Stage IV disease.[13]

Treatment for colorectal cancer is often multidisciplinary. Stage I, II and III disease are most often treated with surgical excision. Final pathology results determine the need for adjuvant therapies, particularly systemic chemotherapy. Due to the anatomic constraints of the pelvis, rectal cancer is approached differently than colon cancer. Rectal Cancer can often require pre-operative, or neoadjuvant treatment with radiation, with or without chemotherapy.[14] Colorectal cancer is unique in that Stage IV disease is often still treated aggressively and depending on the extent of disease treatment may have curative intent.[14] There is strong evidence that resection of liver metastases can give lead to prolonged 5-year survival.[15-17] It is also common practice to resect isolated lung metastases.[14,18] Similarly, isolated peritoneal spread is selectively treated with cytoreductive surgery and heated intra-peritoneal chemotherapy.[19]

c. Association of Inflammatory Bowel Disease and Colorectal Cancer

The presence of IBD increases the risk of developing colorectal cancer. The risk is associated with increased duration of colitis. The rates of developing cancer at 10, 20, and >20 years of colonic inflammation are 1-2%, 2-8% and 5-18%, respectively. [20,21]

The increased risk of CRC was initially identified in ulcerative colitis and was not thought be increased in the Crohn's population; however, it has also been identified that in Crohn's patients with colonic involvement, the risk of CRC is similar to that of ulcerative colitis patients.[22,23]

A meta-analysis evaluating over 116 articles suggested that the prevalence of CRC in the setting of ulcerative colitis is 3.7% and in patients with pancolitis, that prevalence increases to 5.4%. By comparison, the prevalence of CRC in the non-IBD population is approximately 0.4%. [24] This also highlights the relationship between pancolitis and increased risk of malignancy. [23] While there is colonic involvement in all ulcerative colitis patients, in Crohn's many patients have disease isolated to the small intestine or other parts of the gastrointestinal tract but will have no inflammation of the colon. In the absence of colonic disease, these patients do not have the same increased risk of developing CRC as Crohn's patient with colonic involvement. However, they do have an increased risk of developing adenocarcinoma of the small bowel.[25] Guidelines for colonoscopic evaluation for the IBD population are dependent on the extent and duration of colitis. Screening is initiated 8-10 years after the development of colitis and as time elapses the duration between colonoscopies decreases because the risk of developing colorectal cancer increases.[26]

The etiology of CRC in the IBD population shares many properties with that of the non-IBD population. In sporadic CRC, the development of cancer follows the 'adenoma-carcinoma sequence', where a sequence of mutations occurs leading to colonic adenomas, or polyps, which then acquire more mutations leading to dysplasia and then infiltrative malignancies.[27] A similar pathway is thought to lead to CRC in the IBD-associated CRC population. However, there is some

thought that the rate at which this pathway progresses from dysplastic to malignant tissue is expedited. Known mutations in the CRC pathway such as loss of APC may happen later in the IBD-associated CRC compared to sporadic CRC while p53 mutations which are usually later in the sporadic pathway may happen earlier in the IBD-associated CRC compared to the sporadic CRC patients. Additionally, rather than a few foci of dysplasia arising in a single adenoma in sporadic CRC, in the setting of colitis, there is felt to be a 'field defect', leading to multifocal dysplasia.[28-30] This can lead to multiple primary tumors occurring simultaneously.

Brackmann et al. has defined two phenotypes of CRC in the setting of IBD. They identified patients as either having "widespread neoplasia" where dysplastic tissue was identified distant from the primary tumor, or "localized neoplasia" where dysplastic tissue was only identified in the tissue surrounding the tumor and not elsewhere. They found that 25% of patients fit in the localized neoplasia group. These patients tended to be older, have a shorter duration of colitis, and were less likely to have active disease at the time of CRC diagnosis, compared to those with "widespread neoplasia". [31] They identified that the mortality rate ratio of "widespread neoplasia" compared to "localized neoplasia" was 4.9 (95% CI 1.05–23.73, p=0.043) implying that the "widespread neoplasia" phenotype has a worse prognosis despite controlling for important prognostic factors.[32] They recognized that patients with IBD-associated CRC had increased mortality when compared with those with sporadic CRC; however, when they compared the phenotypes to sporadic CRC, there was an increased mortality rate ratio of 4.3 (95% CI: 2.8–6.4, $p< 0.001$) with the "widespread neoplasia" phenotype. There was no statistically significant difference when comparing the "localized phenotype" to sporadic CRC.[32] This suggests that IBD-associated CRC is likely not a single entity but has variable behaviour based on multiple patient factors.

In the setting of active inflammation, the cyclooxygenase (COX)-2 pathway is activated along with other inflammatory cytokines. Increased COX-2 expression has been found in polyps and adenocarcinoma of the colon.[33,34] Inflammation can also lead to increased presence of Reactive Oxygen Species (ROS) which can result in p53 and mismatch repair mutations.[28] These risk factors for developing malignancy are increased in the milieu of chronic inflammation seen in colitis. Studies have tried to elucidate if decreasing inflammation with agents such as 5-ASA can prevent colorectal cancer development, however no definite risk reduction strategy is supported beyond screening colonoscopy. [35-39]

Inflammatory Bowel Disease is also associated with an increased risk of malignancy outside of the colon including cancer of the small bowel, biliary tree, lymphoma, skin, cervix and urinary tract. The presence of primary sclerosing cholangitis, which is an extra-intestinal manifestation of IBD, increases an individual's risk of cholangiocarcinoma. Moreover, the presence of primary sclerosing cholangitis in the setting of IBD also increases the risk of developing colorectal cancer.[40] Primary sclerosing cholangitis is seen in both subtypes of IBD, however the association is stronger with ulcerative colitis. It is identified in up to 14% of ulcerative colitis patients and 3% of Crohn's disease patients.[41,42] The risk of CRC is thought to be higher in ulcerative colitis-associated primary sclerosing cholangitis, compared to in Crohn's disease. The risk of CRC at 20 years of disease is estimated to be 30%. [43] The mechanism of increased risk of CRC with primary sclerosing cholangitis is not known. A positive family history for CRC is a risk factor for developing CRC in the setting of IBD as well as in sporadic CRC.

The reported prevalence and risk of IBD-associated CRC varies in the literature. Some of this variability may be due to the methods of data collection and cohort definition. The reporting of incidence rates from IBD referral centres as compared to population-based studies can inflate the magnitude of risk.[44] Patients from referral centres tend to have higher incidence of malignancy, which is likely related to referral bias.[44] Additionally, the country of origin of the studies may play a strong role in the discrepancies. IBD prevalence is associated with geographic location, with variation within and between countries.[45] This suggests an environmental component to the development of IBD. It is also possible also that the behaviour of IBD, local screening guidelines and treatment protocols vary by region, thus altering the incidence and behaviour of colon cancer in the setting of inflammatory bowel disease.

d. Treatment Factors for Colorectal Cancer in Inflammatory Bowel Disease

Guidelines for colorectal cancer treatment do not suggest any specific differences in therapy based on if a patient has IBD;[14] however, it is possible that the treatments received are different in the IBD-associated CRC patients as compared to the sporadic CRC patients.

The IBD population has unique features related to their disease process as well as the medications used to treat their disease. They are often taking corticosteroids or other immunosuppressant medication which can impact risk of malignancy development and risks of treatment.[46] For example, IBD patients on steroids who undergo colon resection are at an increased risk of re-

operation and anastomotic leak.[47] These complications can result in prolonged hospitalizations, and may preclude patients from getting adjuvant chemotherapy within a therapeutic window.

Axelrad et al. identified that patients with IBD on chemotherapy for CRC were more likely to need dose adjustments and treatment delays than those with sporadic CRC.[48] Chemotherapy regimens for CRC usually include a fluorouracil backbone; which can have significant gastrointestinal toxicity, with diarrhea present in approximately 50% of patients.[49] A treating physician may be concerned that a patient's baseline symptoms from IBD may be exacerbated by treatment and may adjust or withhold chemotherapy to prevent this.

Another retrospective study evaluated 44 patients who had IBD-associated CRC resected and underwent adjuvant therapy. Propensity score matching was performed with sporadic CRC patients and matching was based on age, surgery intent, site of CRC, grade, and stage. There was no statistically significant difference in overall survival, recurrence or disease free survival.[50] Nio et al. retrospectively evaluated 29 patients with IBD who received chemotherapy for resected or metastatic colorectal cancer. This study similarly identified high rates of dose adjustments. This study was focused on studying efficacy of treatment. In the adjuvant setting, the 5-year disease free survival was 78%. In the palliative setting, an objective response rate of 15% was seen, with a disease control rate of 77%. Although the adjuvant therapy outcomes are similar to the sporadic population, in the palliative setting they do report a median survival of 315 days which is lower than those reported in modern literature for metastatic colorectal cancer.[51,52] The small size of this study limits the ability to draw any conclusions.

Additionally, the use of novel treatments such as immunotherapy is controversial in patients with autoimmune conditions, such as inflammatory bowel disease.[53,54] Although in colorectal cancer immunotherapy is not routinely used, for some patients with tumor microsatellite instability, immune therapy is thought to be an effective treatment strategy.[55] However, given that IBD is an autoimmune condition, there is fear that using these drugs would lead to a flare of the autoimmune condition and in these conditions a severe flare can be life threatening.[53,54,56] This concept is being challenged with more frequent use of immunotherapy in the setting of autoimmune conditions.[57]

e. Survival Outcomes

Survival outcomes reported for CRC patients with IBD are inconsistent. Reynolds et al. recently reported a meta-analysis of 20 papers evaluating clinicopathologic outcomes in IBD-associated CRC compared to sporadic CRC. They found that IBD had no impact on overall survival (OS) (OR 1.1, 95% CI 0.41-2.95, p=0.842). They found that IBD related CRC was more likely to present as poorly differentiated, and with synchronous lesions, and less likely to arise in the rectum when compared to sporadic CRC.[58] They did not identify increased rates of T3/T4 disease, nodal positivity or metastases. This meta-analysis did not address the risk of recurrence.[58] Kiran et al. retrospectively reviewed all patients in a referral centre who underwent resection for colorectal cancer in the setting of IBD. They identified 240 patients and were able to match them 1:2 to controls with sporadic CRC. They did not see a difference in disease free survival, or local

recurrence.[59] Some suggest that IBD is protective, possibly because patients participate in surveillance programs, hence cancers are detected earlier.[37,60]

Conversely, a single centre that prospectively followed their patient population with IBD, a cohort of IBD patients with CRC were compared 5:1 to a matched cohort of patients with sporadic IBD. These patients all underwent resection of the primary tumor. In this study, the local recurrence was higher in the IBD population and there was a statistically significant decrease in 5-year survival (48.6% vs 67.1%, p=0.02) in the IBD population. The worse survival was seen when they controlled for age, stage, gender, site of the primary tumor and the date of resection. This study did not find any difference in outcomes related to age.[61] A Japanese population-based study identified that patients with ulcerative colitis associated CRC had poorer survival when presenting as Stage III CRC whereas at earlier stages, survival was similar.[62] Results from this study should be interpreted with caution as the study had 169 cases of ulcerative colitis associated CRC out of a total of 108,536 CRC cases (0.15%). North American literature suggests that IBD-associated CRC makes up 1-2% of CRC patients. This difference in the prevalence may reflect differences in the behaviour of IBD in the Japanese population.

A recent registry-based study evaluated the prognostic implication of colorectal cancer liver metastases in the setting of inflammatory bowel disease. They did not identify a statistically significant difference between IBD-associated and sporadic CRC patients with regards to overall survival (HR, 0.95; 95% confidence interval [CI] 0.57-1.57) and recurrence free survival (HR, 1.07; 95%CI 0.68-1.68; P = 0.780).[63] However, they did identify a higher proportion of patients

with extra-hepatic disease in the IBD-associated patients compared to sporadic patients (28.6% vs 8.3%; $P < 0.001$).

f. The Ontario Crohn's and Colitis Cohort

The Ontario Crohn's and Colitis Cohort (OCCC) is a population-based surveillance cohort of patients within the Institute for Clinical and Evaluative Sciences (ICES) that was created using a validated algorithm.[64] [65] It was initially developed in the setting of pediatric IBD and was then expanded to an adult population and has been used to study incidence, prevalence and treatment patterns of IBD in the province of Ontario.[6,64-66] The algorithm identifies patients having Crohn's disease or ulcerative colitis based on a combination of procedures performed (endoscopy), clinical visits and hospitalizations and their associated International Classification of Disease (ICD) codes. The algorithm's ability to identify patients with IBD has a sensitivity of 92.3% (95% CI 89.2-94.5) and a specificity of 99.1% (95% CI 98.1-99.6).[65]

This surveillance cohort allows us to evaluate, at a population level, the prognostic significance of IBD in colorectal cancer.

g. Research Questions

Given the high prevalence of both CRC and IBD in Ontario it is important to describe the survival outcomes of patients with IBD-associated CRC. This is done at a population level to avoid selection bias or referral bias. The aim is to answer the following questions:

1. Do patients with IBD-associated CRC present at an earlier, later, or similar stage to patients with sporadic CRC?
2. Are there pathologic differences, beyond stage, between sporadic and IBD-associated CRC?
3. When controlling for stage, do patients with IBD have similar survival to patients with sporadic CRC?
4. What factors predict survival in these patients?
5. Are patients with IBD "undertreated" with respect to surgery, chemotherapy or radiation?
6. Are treatments in IBD patients as efficacious as they are in sporadic CRC patients?
7. Are the costs of care similar between IBD-associated and sporadic CRC? If there is a difference, what costs make up the majority of the difference?

h. Rationale for population-based study

It has been established that inflammatory bowel disease is associated with increased rates of developing CRC; however, the literature on outcomes such as survival and treatments received are conflicting. Prior studies are limited by being from single centres, having small sample sizes, or missing staging and treatment information. To address these limitations, our study compares

patients with IBD-associated CRC to those with sporadic CRC using a large population-based cohort from Ontario, Canada.

Methods:

a. Administrative Data Sources and Linkage

The Institute for Clinical Evaluative Sciences (ICES) is an Ontario-based organization that links multiple administrative databases for research, which are then de-identified to describe patient demographic, treatment and outcome information. Because Ontario has a universal, single payer, health care system, the databases provide comprehensive coverage of health care diagnoses, treatment and outcomes for all patients in Ontario.[67] Our population based retrospective cohort study was derived from the Ontario Cancer Registry, including patients diagnosed with CRC between 2007-2015. The initial cohort was intended to be from 2000-2015; however Colorectal Cancer staging information was absent a very high proportion of cases in the Ontario Cancer Registry until 2007. Stage was felt to be an essential prognostic factor to control for and therefore the cohort was restricted to 2007 onwards. The entire initial cohort (2000-2015) was used to verify findings that were not dependent on stage. International Statistical Classification of Disease and Related Health Problem (ICD)-10 codes, which are obtained from the Discharge Abstract Database were used to identify a diagnosis of CRC. Patients documented as having stage 0 cancer, or in situ disease, were excluded. This exclusion was performed as it was felt that stage 0 patients would not undergo cancer treatments and have no risk of metastasis or mortality from cancer and are therefore not the population of interest. The cohort of IBD-associated CRC patients was derived from identified to have CRC who also belonged in the Ontario Crohn's and Colitis Cohort (OCCC).

The Canadian Institute for Health Information Discharge Abstract Database and Ontario Health Insurance Plan physician billings were used to determine surgical interventions, chemotherapy use and radiation use. The Ontario Health Insurance Plan Schedule of Benefits and Fees was used to determine billing codes that would be appropriate for surgical intervention, radiation use and chemotherapy use.

The Ontario Drug Benefit and New Drug Funding Program were used to supplement data on chemotherapy treatments. The Registered Persons Data Base provides details on geographic location, age, and date of death. The following databases were added to complete the costing analysis: National Ambulatory Care Reporting System (Emergency Department use), Continuing Care Reporting System (sub-acute care), and Ontario Mental Health Reporting System (mental health hospitalizations).

Demographic information collected from the above databases included: age, sex, rurality, income quintile, year of diagnosis, Deyo-Charlson Comorbidity Index[68], site of primary tumor, presence of metastases, stage, Tumor (T)-category, Nodal (N)-status[11], location of metastases if present, and grade of tumor. Lymph node ratio was calculated as number of positive nodes divided by the number of nodes harvested. As part of the de-identification process, age was provided in pre-specifiedage groupings (defined by ICES as: 18-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85+), and this categorization was used as a continuous variable in regression

analysis. Ages were further grouped into four categories (<50, 50-64, 65-80, >80) for presentation of results in figures and tables.

Income quintile is determined by the median income of the population within an individual's postal code. Site of primary tumor is determined by ICD-10 codes that identify the location of the tumor. Due to some categories having small numbers, some locations were grouped together to protect individual patient information. Missing data for tumor (T) category, nodal (N) category and grade were called "Unknown" and were categorized together for regression analysis.

In the IBD population, the IBD type was defined as Crohn's Disease, Ulcerative Colitis and Unclassified as per the OCCC validated criteria.[6] Data was de-identified and any results that had very small numbers ($n \leq 5$) could not be reported to protect confidentiality.

b. Outcomes Assessed

Our primary outcome measure was overall survival from time of CRC diagnosis until the date of death. Patients alive as of November 30, 2017 were censored on the date which the patient last had contact with the healthcare system.

Secondary outcome measures included treatments received (including surgery, radiation and chemotherapy) and publicly-provided health care costs. Thirty day post-operative mortality was assessed in Stage I-III patients undergoing resective surgery. Surgery was considered resective if

a billing code for a bowel resection was performed; if the operation was for fecal diversion alone, surgery was considered non-resective.

c. Supportive Analyses

Rates of treatment were evaluated in an exploratory subgroup of stage III patients as it was hypothesized that differences in survival may be attributed to differences in receipt of adjuvant therapy, which is most often indicated in the stage III population.[14]

Analysis of patients Stage I, II and III undergoing resective surgery was done as a supportive secondary analysis in order to determine if differences in outcomes were apparent between IBD-associated CRC and sporadic CRC patients in those who received resective surgery. Surgery in these individuals was considered curative intent and included in this analysis if surgery was 90 days prior to or 180 days after the date of diagnosis. This time frame was selected in order to include patients who underwent neoadjuvant therapies for rectal cancer and would have definitive surgery several months after diagnosis. Although some patients who were initially Stage IV may undergo definitive resection of the primary cancer and metastases, they were not included in this subgroup analysis because their management is heterogeneous and within the administrative data it is challenging to distinguish curative intent treatment from palliative procedures.

d. Cost evaluation

Costs included hospital admission, surgery, outpatient clinic and emergency department visits, physician billing, drugs covered by the provincial plan, amongst others.[69] Cost is determined using a macro for ICES data called GETCOST. This method pulls estimated costs for an average individual in Ontario for each encounter or use of the health care system. The costs calculated are not specific to the individual patients in the study but are an estimate of the costs that the individuals in the study would incur based on their health care visits, hospital stays, drug use, long term care admission, home care use, assistive devices used, etc. These costs are weighted by a base rate, dates of exposure and some have an age or gender multiplier.[70] Sum of costs were determined for the first year from diagnosis and then up to years two, five and ten from time of diagnosis of colorectal cancer. The index date was considered the date of diagnosis.

e. Statistical Methods

Descriptive statistics were used to summarize patient and disease characteristics as well as outcomes. The Pearson χ^2 and Wilcoxon rank sum tests were used to compare patient and disease characteristics between patients with and without IBD. Univariable regression analysis was performed to determine the potential prognostic value of variables. A full multivariable regression model was also constructed, meaning that all factors were included in the model, to assess the impact of IBD adjusted for all other potential variables. In the regression analysis, tumor (T) status and nodal (N) status were not included because they convey similar information as Stage and including both would lead to multicollinearity. However, to verify that these factors were not

driving outcome, an additional regression was performed to determine their impact on the multivariable analysis. The regression was also done in the subgroup of Stage I, II and III patients who underwent resective surgery.

Assessment of potential interactions between IBD and other factors was evaluated. Bi-variable and tri-variable models were created with factors that were found to be prognostic. Cox proportional hazards regression model was used to evaluate factors potentially prognostic of survival and logistic regression was used to evaluate potential prognostic factors of treatment.

Product-limit survival estimates were performed for all patients, and then repeated when broken down by age and by stage.

Costs were collected as a cumulative yearly patient costs, adjusted for inflation to the year 2015/2016 and were compared with Wilcoxon Rank Sum test. Breakdown of allocation of costs in the first two years from diagnosis of CRC was reviewed. All analyses were two-sided and performed at the $\alpha=0.05$ level of significance.

f. Ethics Approval

Hamilton Integrated Research Ethics Board approval was obtained for this study.

Results

Patient Demographics

In the initial cohort, when including patients from 2000-2015, there were a total of 114 579 patients, and 1307 (1.1%) had a diagnosis of IBD. After restricting the cohort to 2007-2015 when staging information is more complete, 67,137 patients were identified as having a new diagnosis of CRC. Of these patients, 783 (1.2%) had a diagnosis of inflammatory bowel disease and were included in the OCCC cohort at the time of CRC diagnosis. In those with IBD, 293 (37.4%) were classified as Crohn's disease, 470 (60.0%) were classified as ulcerative colitis, and 20 (2.6%) had unclassified inflammatory bowel disease. The median age range at diagnosis of CRC in the IBD-associated CRC population was 55-59 years and in the sporadic CRC population was 70-74 years old ($p<0.001$).

In both IBD-associated and sporadic CRC, grade 2 tumors were most common (64.9% and 52.1%, respectively); however, in those with known tumor grade, patients with IBD were more likely to have grade 3 or grade 4 tumors (29.2%) than patients without IBD (13.6%) ($p<0.001$). In patients where stage was known, there was no significant difference in the overall stage (I-IV) at diagnosis of CRC between the IBD and non-IBD population ($p=0.65$). In those with known tumor (T) status, the IBD group had more T4 tumors (26.9%) compared to the non-IBD population (19.0%), ($p<0.001$). In those with known nodal category, the IBD-associated and sporadic CRC patients had similar proportions of node negative disease (58.7% vs 59.9%, $p=0.57$). However, in the node positive patients, the proportion of patients with four or more lymph nodes involved (N2-3 disease)

was higher in the IBD-associated CRC group than in the sporadic CRC group (41.9% vs 33.3%, p=0.006). (Table 1) In the node positive patients, the median lymph node ratio (positive nodes: nodes examined) was 18.8% in the IBD-associated CRC patients and was 14.6% in the sporadic CRC patients, (p=0.28). There was no significant difference in the rate of right sided tumors in the IBD vs sporadic CRC population (38.1% vs 38.4%, p=0.43); however, the IBD population was more likely to have rectal primaries (27.5% vs 23.6%, p=0.003).

Median Deyo-Charlson Score was similar in the IBD-associated CRC population (4 in both, p=0.27). Patients with IBD-associated CRC tended to live in areas of higher income quintile compared to those with sporadic CRC (p<0.001). (Table 1)

Survival Outcomes

Five-year survival in IBD-associated CRC patients was 52.5% (95% CI 48.5-56.3) and 52.6% (95% CI 52.2-53.0) in those with sporadic CRC (p=0.86). Median survival in the IBD-associated CRC patients was 70.7 months (95% CI 55.3-84.3) and was 67.2 months (95%CI 65.9-68.7)in the sporadic CRC group. In patients who had Stage I, II or III disease that underwent resective surgery, 30-day post-operative mortality was 2.7% (95% CI 1.6-4.7%) in IBD-associated CRC and 2.9% in sporadic CRC (2.7-3.1%), p=0.31. (Table 1)

Results evaluating the association of potentially prognostic factors on overall survival from univariable Cox regression models are presented in Table 2. The presence of IBD at diagnosis of CRC was not significant in the univariable regression model (Hazard Ratio (HR)=1.01, 95% CI 0.91-1.13, p=0.80). However, in the multivariable model, the presence of IBD was found to be a significant predictor of death (HR=1.45, 95% CI1.29-1.63, p<0.001) after adjusting for other variables. Other factors that were predictive of survival were younger age, lower stage, lower tumor grade, lower comorbidity, and increased income quintile, and increase in year of diagnosis (Table 2). When stage was replaced by T and N status, the impact of IBD on survival was similar in the multivariable analysis (HR 1.57). Interaction tests showed a significant interaction between IBD status with age (p<0.001). A significant interaction between IBD status and stage (p<0.001) occurred if age was included in the model but did not exist if age was not included in the model (p=0.13). No other significant interactions were identified. Bivariable, tri-variable and multivariable regression models were created with IBD status, age and stage to further understand the relationship of these three factors on survival. When IBD status and age are included in a bivariable model, the Hazard Ratio for IBD increased from 1.01 (95% CI 0.91-1.13) in the univariable model to 1.37 (95% CI 1.24-1.53). The addition of stage increased this value to 1.46 (95% CI 1.31-1.62) and the remaining variables increased the hazard ratio of 1.45 (95% CI 1.29-1.63). The presence of this interaction indicates that results need to be investigated within subgroups (age and stage) for interpretation.

Survival by Age

For ease of interpretation, age was categorized into four groups (<50, 50-64, 65-80, ≥80). CRC patients above the age of 65 did not have significantly different five-year survival in the IBD-associated compared to sporadic CRC groups [age 65-79: 59.0% (95% CI 51.4-65.9) vs 59.5% (95% CI 58.9-60.1), p=0.71, age ≥80: 33.9% (95% CI 24.4-43.6) vs 34.6% (95% CI 33.8-35.4), p=0.78]. However, in patients under 65, statistically significant reductions in five year survival were seen in the IBD-associated CRC group compared to those with sporadic CRC [age 18-49: 56.8% (95% CI 49.4-63.5) vs 71.4% (95% CI 70.0-72.7), p<0.001, age 50-64: 61.8% (95% CI 55.6-67.4) vs 69.6% (95% CI 68.9-70.4), p<0.001] (Table 3, Figure 1).

Because stage was not included in this model, the initial cohort data from 2000-2007 was added to verify this finding to increase the size of the sample. The same pattern was identified in the larger cohort.

Survival by Stage

When comparing all stages, overall survival was similar between IBD and sporadic CRC patients. (p=0.86). When breaking down patients by stage alone, patents diagnosed with Stage II and IV CRC had similar survival in the IBD-associated and sporadic CRC groups. Stage I IBD-associated CRC patients had slightly better survival than sporadic CRC patients (5-year survival of 85.2%, 95% CI 78.2-90.0 versus 80.1%, 95% CI 79.4-80.8). Conversely, Stage III IBD-associated patients

had worse survival compared to those with sporadic CRC (5-year survival of 52.5%, [95% CI 45.0-59.5%] versus 61.2%, 95% CI 60.5-62.0%), (Figure 2).

Table 4 shows the hazard ratio of death for IBD-associated vs sporadic CRC patients broken down into age and stage categories. The effect of stage on the difference in survival is generally lost when age is introduced. In all patients under 65, IBD patients have significantly increased HR for death, regardless of stage. The exception is Stage I patients aged 50-64, where the HR is 0.6 (95% CI 0.2-1.8), p=0.33. Additionally, those under 50 with unknown stage did not have a statistically significant difference in survival HR 1.4 (95% CI 0.7-2.6), p=0.38.

In patients over 65, there is no statistically significant difference in survival at any stage between patients with IBD-associated and sporadic CRC. However, a trend toward worse survival in stage III patients with IBD-associated CRC is observed (HR 1.5 95% CI 0.99-2.3, p=0.054 for patients aged 65-79 and HR 1.5, 95% CI 0.98-2.4, p= 0.059 for patients over 80).

Treatments

IBD was associated with increased use of chemotherapy (48.4% vs 40.2%, p<0.001), increased rates of non-resective surgery (4.0% vs 2.4%, p=0.004) and a decreased rate of having no treatment (8.2% vs 13.0%, p<0.001). There was no significant difference in the use of radiotherapy and resective surgery between those with IBD-associated and those with sporadic CRC (see Table 1).

After adjusting for other variables (sex, age, income, charlson comorbidity index, rurality, income quintile, year of diagnosis, stage and sites of metastases) IBD status was significantly associated with increased rates of non-resective surgery (Odds ratio (OR) 1.84, 1.25-2.70, p=0.002), decreased likelihood of having no treatment (OR 0.69, 0.52-0.92, p=0.013); IBD status was not statistically significant but trended towards decreased rates of chemotherapy (OR 0.85, 95% CI=0.72-1.02, p=0.079) and radiotherapy (OR 0.84, 0.68-1.02, p=0.079); IBD was not associated with rate of resective surgery (0.98, 0.80-1.21, p=0.87).

When stratified by age (<50, 50-64, 65-89, ≥80) there was no difference in any modality of treatment received between IBD-associated and sporadic CRC patients (Table 3).

Treatment adjusted for stage

Treatment patterns were evaluated according to stage at diagnosis. The use of radiotherapy and resective surgery was similar between the IBD-associated and the sporadic CRC population, with the exception of higher rates of resective surgery in stage I patients with IBD-associated CRC (87.5%) compared to sporadic CRC patients (79.3%), p=0.011. When broken down by stage, the IBD-associated CRC population was more likely to get systemic chemotherapy at every stage. The exception is in patients with unknown stage where there was no statistically significant difference in chemotherapy use. (Table 5)

Supportive Analyses:

Stage III Patients

Amongst stage III patients who received chemotherapy, IBD was associated with poorer survival. Five-year survival was 57.9 % (95% CI 49.1-65.7) in IBD-associated CRC and was 70.7 % (95% CI 69.6-71.5) in sporadic CRC, p=0.001. In those who did not receive chemotherapy, there was no statistical difference in survival [34.8% (95% CI 21.5-48.4) vs 41.2% (95% CI 39.8-42.6)], p=0.13 (Table 6). Worse survival in IBD patients who received chemotherapy was consistent across all age groups (18-49: HR=2.04, 95% CI1.23-3.37, p=0.006, 50-64: HR=2.33, 95% CI 1.64-3.31, p<0.001, 65-79: HR=1.63, 95% CI 0.98-2.71, p=0.060) except in the 80+ age group (not calculated since only two Stage III patients over 80 had IBD and received chemotherapy).

Patients with Stage I-III resected disease

In patients with Stage I, II and III colorectal cancer who underwent resective surgery, demographics were similar to the cohort that included those with Stage IV and Unknown Stage. The median age range at diagnosis was younger in the IBD-associated CRC patients (60-64) as compared to the sporadic CRC patients (70-74), p<0.001. The resected IBD group is slightly older than median age of the whole cohort (55-59). Stage at diagnosis was not different between IBD-associated and sporadic CRC patients. There was no difference in the rate of right sided (versus

left) or rectal cancers between IBD associated and sporadic CRC in those with Stage I-III disease that underwent resection.

IBD-associated CRC patients were more likely to receive chemotherapy (45.5% vs 39.2 %, p=0.005). There were no differences in receipt of radiation (19.4% vs 20.7%, p=0.49), (Table 7). When stratified by age groups, there were no statistically significant differences in treatment between the two groups. (Table 8)

There is no significant difference in survival with median survival being 110.0 months (95% CI 96.9-not reached) in the IBD-associated group and 101.5 months (95% CI 100.3-103.3) in the sporadic group. Five-year survival in IBD-associated CRC was 65.0% (95% CI 59.9-69.7) and was 68.5% (95% CI 67.9-69.0) in the sporadic CRC population. (Table 7)

Multivariable analysis was performed in this subgroup and again demonstrated that the presence of IBD was associated with worse survival with a Hazard Ratio of 1.59 (95% CI 1.33-1.89, p<0.001). Increasing grade, stage, and year of diagnosis are significantly prognostic of worse survival. Being of higher income, being female, and not being rural were protective. (Table 9)

Given the known interaction with age in the complete cohort, survival outcomes were broken down by age groups and identified a similar pattern. In patients under 65 who underwent resective surgery, five-year survival was significantly lower in IBD-associated CRC. In patients 18-49, 5

year survival was 75.4% (95% CI 64.4-83.4) in the IBD-associated patients and 85.5% (95% CI 83.9-87.0) in sporadic CRC, p=0.005. Similarly, in patients aged 50-64 there was an 11.5% difference in 5-year survival (p<0.001). In those over 65, there is no statistically significant difference in survival between patients with IBD associated CRC and those with sporadic CRC. (Table 8, Figure 3)

Subtypes of IBD

When comparing subtypes of IBD, a higher proportion of ulcerative colitis patients were male (61.3%) compared to in the Crohn's patients (53.9%), p=0.045. Ulcerative colitis patients were older at diagnosis than Crohn's patients (median range 60-64 versus 55-59, p=0.023). Stage at presentation, tumor status and nodal positivity were similar between Crohn's and Ulcerative Colitis. Treatments were similar between groups; however, Crohn's patients were more likely to receive radiation (28.7% vs 19.2%, p=0.003). Five-year survival was 50.6% (95% CI 48.4-56.5) in Crohn's Disease versus 59.9% (95% CI 55.1-64.4), in ulcerative colitis (p=0.017) (Table 10).

Costs

In the two years after diagnosis of CRC, the median cost of care (Canadian Dollars) for a patient with IBD-associated CRC is $53256, and for a patient with sporadic CRC it is $46293 (p<0.001). The inpatient costs of IBD patients ($33,591) are significantly higher than those with sporadic CRC ($25,149), (p<0.001) and make up the largest difference in cost between the two groups. Outpatient costs, Emergency Department costs and OHIP billings are all higher in the IBD-associated CRC patients; whereas Ontario Drug Benefit costs are higher in the sporadic CRC

patients (Table 11). There were significantly increased costs of care in year 1, and up to years 2, 5 and 10 for the IBD-associated CRC population. After exclusion of rectal cancers as these are higher in the IBD group, the median costs decreased in both groups but were still significantly higher in the IBD population (Tables 12a, 12b).

In the subset of patients with Stage I-III CRC who underwent resective surgery costs are significantly higher in the IBD population in all years. The exclusion of rectal cancers in this group did not change the difference in costs (Table 13a,13b).

Discussion:

a. Differences in the IBD-associated CRC population compared to Sporadic CRC

Baseline Characteristics

In our population-based study in Ontario, several differences in the demographics and outcomes of CRC in IBD as compared to sporadic CRC were identified. Regarding baseline demographics patients with IBD-associated CRC were younger, more often male and from higher income quintiles.

Pathologic Differences

In many cancer types, differences in outcomes in various populations are related to stage at presentation. If a patient subgroup is likely to have a delayed presentation, they may have worse oncologic outcomes. This theory was thought to be plausible in the IBD population because symptoms that are typically thought to be caused by a colorectal cancer such as pain, obstruction and bleeding, may be ignored by an IBD patient, as they would attribute said symptoms to their IBD. However, within this study, there was no difference regarding initial stage at presentation between IBD-associated and sporadic CRC patients. One possibility is that on balance, stage is similar because some present very late with ignored symptoms, while others are having frequent

screening colonoscopy and are therefore identified very earlyHowever, it could be that these factors do not play a role and these patients present at the same stage.

Stage is determined by the American Joint Council of Cancer (AJCC) and is comprised of three components- the tumor (T)-status, the nodal (N) status, and the presence of distant metastases (M).[11] The AJCC staging classifies tumors by their T, N and M categories to give a "best stage" for a patient. However, we must consider that a patient may have a tumor that is invading the muscularis propria (muscle layer of the bowel wall) with no nodal disease nor metastases (T3 N0 M0) or they could have a tumor that is locally perforated with no nodes or metastases, making it T4b N0 M0. Both would be classified as Stage II disease but based on the T status may have different behaviour. In a small series by Elias et al. having a perforated (T4b) tumor was associated with a 33% chance of peritoneal carcinomatosis 13 months after initial surgery.[71] This disease is often not curable.

Despite differences in risk of recurrence, when evaluating stage alone these patients would not be classified as different. Therefore, it is important to identify pathologic differences beyond stage that may be prognostic in the IBD population for worse oncologic outcomes. We have identified that the IBD-associated CRC patients are more likely to have T4 tumors and are more likely to have high grade tumors (Grade 3 or 4 versus Grade 1 or 2). Although the rate of nodal positivity is not higher, in those with positive nodes, we do see a higher burden of nodal disease (more N2-3 disease) in the IBD-associated patients. A prognostic feature that was considered was the "lymph node ratio", which examines the ratio of nodes positive relative to nodes harvested. This was not

statistically different between sporadic and IBD-associated CRC. This must be interpreted with caution however, because IBD patients often undergo larger colonic resections (ie total colectomy, rather than segmental resection) due to their underlying IBD; thus, harvesting more benign lymph nodes and decreasing the ratio. We have identified that although stage at presentation is not significantly different, there may be some pathologic differences at presentation that can drive the difference in survival outcomes. When evaluating patients with IBD with lower stage disease, it is important to recognize that these high-risk pathologic features may be present, despite the low stage and they may herald a worse prognosis. However, despite these high-risk features being present more frequently in the IBD population, when they were included in multivariable analysis, the impact of IBD on survival did not change. This suggests that these factors alone are not driving the worse survival for IBD patients.

A recent area of interest in colorectal cancer is tumor sidedness. Recent evaluations of large trials looking at metastatic colorectal cancer have shown predictive and prognostic significance of the location of the primary tumor.[72] Right sided tumors are defined as being from the cecum to the splenic flexure, while left sided tumors are anything distal to the splenic flexure, including the rectum. There are theories that these are embryologically different and have different microbiomes. A meta-analysis by Petrelli et al. identified that in metastatic CRC, left sided tumors have a better prognosis than right sided tumors, HR 0.82 (95% CI 0.79-0.84).[72] In the IBD-associated CRC patients, there was not a difference in right sided tumors compared to those with sporadic CRC (38.4% vs 38.1%, p=0.43). The multivariable analysis was performed with tumor location by ICD code, rather than sidedness; however, a clear pattern of outcome related to location of the primary was not identified. When looking at patients with resected Stage I-III disease in the

multivariable analysis, there was no pattern identified where site of the primary impacted survival other than tumors of the rectosigmoid (ICD C19) having a slightly improved survival compared to other sites.

When calculating the difference in right versus left sided tumors, the rectal cancers were not included, and there was a statistically significant (p=0.013) increase in left sided tumors in the sporadic population. However, we identified a higher proportion of rectal cancers in the IBD-associated CRC population and when these are included in the left sided tumors, the significance of this is lost (p=0.43). The latter would be in keeping with traditional definitions of left sided tumors. When looking at the supportive analysis of those with Stage I, II and III disease who underwent resection, there is also no statistically significant difference in the side of primary tumor (p=0.072). With this we can infer that any differences in outcome in these groups would be unlikely to be driven by location of the primary tumor. Additionally, the impact of sidedness has not been studied outside of the metastatic setting.

b. Outcomes related to patient age

In the multivariable analysis, we see that increasing age is associated with a worse prognosis [Hazard Ratio 1.23 (95% CI 1.22-1.24)]. One conclusion is that as people age, they are more likely to have worse outcomes with a malignancy. This may be related to other comorbid disease, increased surgical risk, or inability to tolerate adjunctive treatments. However, the interaction of age and IBD was statistically significant and lead to an evaluation of the impact of age on IBD as

a prognostic factor. It was identified that within age brackets, the impact of IBD on survival varied. In patients under 50 and between 50 to 64, survival outcomes were worse for IBD patients compared to sporadic CRC patients within the same age category. This survival difference was seen despite similar rates of surgery, chemotherapy and radiation treatments in the two groups, as well as when controlling for stage. In patients within the age brackets: 65-80 and over 80, the outcomes were similar in the IBD-associated and sporadic CRC groups.

When a similar analysis was performed in Stage I, II and III patients who underwent resective surgery, those under 65 had statistically worse survival which was similar to the entire cohort. In those above 65, although not statistically significant, there was a more noticeable trend toward worse survival in the IBD-group compared to the complete cohort. It appears that the impact of age, although still present, may be dampened in those who undergo curative intent resection.

The finding that IBD-associated CRC is diagnosed at a younger age than sporadic IBD is consistent with the literature[21,73,74] However, these studies have not reported age-related differences in survival outcomes and the interaction of age and IBD status is a unique finding in our study. There is a theory in the literature of two dominant phenotypes of CRC in IBD, one in the younger patients who have diffuse dysplasia which has a worse prognosis, and those in older patients with more focal disease which behaves more like a sporadic CRC. [32,75] [31] The results of this study support that there is an age-related difference in outcomes. Within this study, we do not have the information about the patients' severity of colitis, or other dysplasia identified within the colon and cannot assume that the age-related difference is in keeping with the theory of focal versus

widespread dysplasia. However, this supports that there may be a biologic difference between tumors arising in the milieu of IBD in the young compared to the old patients which may help guide future research.

c. Outcomes related to Stage

When looking at outcomes for patients based on the stage of CRC at diagnosis (regardless of age), we see that those with Stage II and IV tumors tend to have similar survival in the IBD-associated and sporadic CRC groups. However, the very early tumors (Stage I) tend to have better outcomes in the IBD population compared to sporadic CRC. One theory is that IBD patients are often enrolled in surveillance programs with regular colonoscopy. In theory this could increase the chance that on the spectrum of stage I tumors, they may be found earlier than someone without IBD who has a symptomatic stage I tumor. However, this "stage migration" should theoretically apply to all stages and this has not been identified.

Regarding Stage III tumors, there is a trend toward worse outcomes in the IBD-associated CRC, that is statistically significant in those under 65 and approaches significance in those over 65 years old. Stage III patients are those with node positive disease without distant metastases. As seen in the demographics, there is a higher proportion of patients with a higher nodal burden (N2-3, ie $\geq$4 nodes) in the IBD population. It has been established that an increased lymph node ratio (positive nodes: nodes retrieved) is associated with worse disease free and overall survival. [76,77] Although the lymph node ratio was not statistically significant between these groups, we must consider that

lymph node ratio may not be accurate in the IBD population. These patients will often go more extensive colon resection (subtotal or total colectomy) in the setting of malignancy rather than a segmental resection. This will ultimately increase the number of nodes harvested and can falsely lower the lymph node ratio. If we were able to limit the lymph node ratio denominator to the nodes in the segmental draining basin, it is possible we would have detected a higher ratio in the IBD population; however, this would be impossible to do in a retrospective study.

What this difference in nodal burden suggests is that although these patients are all considered Stage III, those with IBD may be presenting with a variant of Stage III disease that has a worse prognosis and this may be contributing to the survival difference.

d) Treatments

Surgery

The primary treatment modality for colorectal cancer is surgical resection. The rate of resective surgery was similar between the two groups with the exception of Stage I patients, where IBD-associated CRC was more likely to have resective surgery (87.5% vs 79.3%). One possible explanation for this is that for some Stage I patients – definitive treatment may involve a local excision which can be done surgically or endoscopically. The definitions used for resective surgery included formal bowel resection, and not local excision or any endoscopic procedures. These were excluded from the definition of resective surgery because these are often the methods of obtaining

the diagnosis and it would be challenging to determine if someone had it for diagnostic or therapeutic purposes within the administrative data. One explanation for the higher rate of resective surgery in Stage I IBD-associated CRC is that IBD patients are not typically candidates for local excision. Given their underlying inflammation and risk of malignancy, any malignant or pre-malignant lesion is more often treated with formal surgical excision rather than a local procedure.

We attempted to assess patients who underwent resective surgery with Stage I, II or III disease to see if the difference in outcomes persisted if patients had curative intent treatment. We did identify that curative intent treatment did not impact the survival differences identified.

Within the group of Stage I, II or III resected cancers, we did not identify a difference in 30-day post-operative mortality between IBD-associated and sporadic CRC. It is important to ensure that survival differences are not driven by early death from surgery, as this would be less likely related to the tumor biology, treatment or cancer related outcomes.

Chemotherapy

We have identified that age also confounds the use of chemotherapy. An initial hypothesis was that treating physicians would be reluctant to prescribe chemotherapy to patients with IBD given their inflammatory condition, gastrointestinal symptoms, or need for immunosuppressive medication. However; our results do not support that theory. In fact, patients with IBD-associated

CRC received chemotherapy at a higher rate than those with sporadic CRC, despite no differences in stage at presentation. However, it is important to note that patients with IBD-associated CRC were generally younger than those with sporadic CRC and when age is controlled for the rates of chemotherapy use are similar between IBD-associated and sporadic patients. We did see a decrease in chemotherapy use with increasing patient age in both groups. This likely is related to patients' general health, ability to tolerate treatment and patient and physician preference.

Patients who are initially diagnosed at Stage III are recommended to undergo surgical resection followed by adjuvant chemotherapy in order to consolidate treatment. This chemotherapy treatment is considered "adjuvant" and is intended to decrease the chance of recurrence and treat any microscopic disease that may be in the circulation.[78] In the stage III population, when patients received chemotherapy, IBD was associated with worse survival than those with sporadic CRC regardless of age group. These results suggest that the survival difference cannot be attributed to IBD patients receiving adjuvant chemotherapy at lower rates than the sporadic population. In Stage III patients who did not receive adjuvant chemotherapy, there was no survival difference. One consideration is that those that did not receive adjuvant chemotherapy are more likely to be older, and this difference is reflective of the age related difference in survival in IBD. Another consideration is that in patients who do not receive adjuvant chemotherapy they may have other medical conditions that preclude chemotherapy use and they may drive their poor survival more than their cancer or their IBD. We also must consider the quality of the care that patients are receiving. If a patient is in an institution or circumstance where they are not receiving adjuvant chemotherapy, it is possible that they are not being referred for chemotherapy at all. This may reflect the quality of care the patient is receiving, including their surgical care. These Stage III

patients may have worse survival and outcomes due to other aspects of their care than chemotherapy use and this could be a surrogate marker for quality of care. A future study identifying the rate of medical oncology referral would be of value to ensure these patients are at a minimum being considered for receipt of adjuvant chemotherapy. Lastly, one consideration is the efficacy of chemotherapy in the IBD-associated CRC patients may be different than in the sporadic population. We know that in certain subgroups of patients, for example those with microsatellite unstable (MSI-high) tumors, 5-FU alone is ineffective, and multi-agent treatment is recommended. Whereas in those with microsatellite stable (MSS) tumors, 5-FU alone – although not currently standard of care- does provide a survival benefit.[79,80] Perhaps a similar phenomenon exists in patients with IBD- where certain regimens that are considered standard are less efficacious due to the biology of the tumors in IBD.

Future prospective studies will be critical in determining if the worse survival is attributed to their relative intolerance of chemotherapy, the lack of biologic response to traditional agents, an immunologic effect, or if their tumor biology is inherently different. Consideration for different agents used for systemic treatment directed at IBD-associated CRC may be required in patients under 65 years old to reach efficacy similar to that seen in the sporadic CRC population.

e) IBD Subtypes

The study was informative regarding the subtypes of IBD and the risk associated with them. Within the OCCC, the prevalence of Crohn's disease was 47.6% and the prevalence of ulcerative colitis

was 48.3%.[6] In our cohort of patients in the OCCC that had a concurrent diagnosis of colorectal cancer, the prevalence of Crohn's Disease was 37.4%, whereas 60% were patients with ulcerative colitis. This likely reflects that the risk of malignancy in the colon is associated with the presence of inflammation of the colon, which is universally present in the ulcerative colitis population; whereas many patients with Crohn's disease do not have colonic involvement.

This study identified that survival in Crohn's disease was significantly shorter than in ulcerative colitis, which may be related to the shorter life expectancy found in Crohn's disease, as compared to ulcerative colitis, in other literature. [81-83] However, it is possible that shorter survival in Crohn's disease is related to the malignancy portending a worse prognosis. One consideration is that unlike ulcerative colitis, Crohn's disease is a transmural disease and we might expect a higher proportion of T4 (full thickness) tumors compared to ulcerative colitis. However, in those with known T stage, no difference in the rate of T4 tumors was identified. Patients with Crohn's disease did have higher rates of radiation treatment. An initial hypothesis was that patients with active inflammation may not be candidates for radiation as it may exacerbate symptoms. It is possible that ulcerative colitis patients had more active colonic inflammation and were not eligible for radiation. Another consideration is that radiation treatment is administered pre-operatively in the setting of more advanced colon and rectal cancers, or post-operatively in the setting of positive surgical margins. We may consider that those with Crohn's disease may have radiologic features that are concerning for being locally advanced or infiltrative, which may increase pre-operative radiation use. We do not have the surgical pathology to inform us on margin status, but it is possible that Crohn's patients had more margin positivity, leading to higher rates of radiation. This could also be

associated with higher recurrence rates and worse survival. This would need to be evaluated prospectively to draw any conclusions.

Knowing that the survival among Crohn's disease is worse, this may drive more aggressive treatment or intensive surveillance for those initially treated with curative intent and may need to be included in discussions about prognosis. Future research should distinguish these two disease types to evaluate if the age-related difference in survival is seen in both subtypes or if it is primarily driven by patients with Crohn's disease.

f) Costs

We also identified that the costs of care for IBD patients with CRC is higher than those with sporadic CRC. Knowing that the IBD population is younger and that inpatient costs make up the majority of cost in the first two years, one might infer that inpatient costs are derived from more aggressive treatments such as intensive care unit stays and more surgical intervention. This is supported by the finding of higher inpatient costs. An increased rate of post-operative complications in the IBD population may also be a contributing factor. A higher rate of rectal cancers was also considered to be a contributor to higher costs, as there are often more interventions and radiation associated with a rectal primary tumor as compared to a colonic tumor. However, when rectal cancers were excluded from the cost analysis the increased costs in IBD-associated CRC persisted.

IBD-associated CRC patients also have higher OHIP Billing costs, outpatient visit costs as well as emergency department costs, which suggests they have an increased number of physician visits compared to the sporadic CRC population. One consideration is that many IBD patients are affiliated with a gastroenterologist who may regularly schedule visits and intermittent investigations. Another consideration is that the OCCC cohort is derived based on an algorithm that includes a certain number of clinical visits. Knowing that the algorithm is highly sensitive and specific for IBD patients; it suggests that the IBD population regularly uses the health care system and may have more baseline health care costs than the average non-IBD patient, irrespective of their cancer diagnosis. The Ontario Drug Benefit costs are lower in IBD-associated CRC compared to the sporadic CRC. This is likely because the Drug Benefit is applied to all patients over 65 years old, therefore more patients in the sporadic population would qualify for this as the median age is higher in this group.

g) Clinical implication and next steps

The findings of this study suggest that there is decreased survival outcomes in young patients who have IBD, compared to young patients who do not have IBD. Certainly this question warrants further study. One consideration is looking for other factors that may be confounding these results. For example- this difference may be driven by a biologic difference in the tumors that develop in these younger patients. Within a prospective database, pathologic features of tumors in young patients (KRAS, MSI, BRAF, etc.) should be collected and compared to the tumors of young patients without inflammatory bowel disease. Next generation sequencing could be performed to characterize differences in the molecular profiles of these tumors if any exist. These features would

be useful in identifying not only differences in the tumors, but in determining targeted agents to use in this population.

One finding that stood out in Table 4 was the high hazard ratio for death in young (<50 years old) IBD patients with Stage I and Stage II disease (HR =3.1 and 3.3, respectively). Stage I and II patients typically have low rates of recurrence but one question we ask is if these patients have higher rates of recurrence in the setting of IBD. Regarding Stage I patients- Cancer Care Ontario states that surveillance imaging and CEA blood levels should be performed at the providers discretion. One recommendation we might make is that in the setting of IBD, surveillance should be routinely performed in Stage I patients. Another future study may investigate whether these patients were receiving follow up imaging to detect recurrence or not.

Regarding Stage II patients- typically adjuvant chemotherapy is recommended only in patients with "high risk features" such as T4 disease, obstruction, perforation etc. One consideration is that a young patient with IBD may in itself be considered a "high risk feature." From this study we cannot conclude that systemic therapy can mitigate the differences in these patients' outcomes- as seen in the Stage III supportive analysis. However, certainly we should consider these patients may need closer surveillance, and potentially adjuvant therapy.

Another question to explore is evaluating the extent of surgery received by the IBD population. Standard recommendation, as mentioned earlier, would be to perform a proctocolectomy in an IBD patient with associated malignancy. However, it is possible that segmental resections are occurring at population level and this may be an area for surgical education and quality improvement if there is a gap in the care being provided to IBD patients with colorectal cancer.

Limitations

Within administrative data causal effect cannot be distinguished and there is potential for unknown confounding. Additionally, our ability to capture details is limited by the retrospective and administrative nature of the data collection. For example, in patients with IBD, we do not know the extent of their colitis, if they were on immunosuppressive medications and the durations of disease. All of which may impact their outcomes. Details about treatment is limited and receipt of chemotherapy is treated as dichotomous (yes or no). We cannot, within this administrative dataset, know the regimen, dose and duration of chemotherapy use, which limits our understanding of prescribing patterns. Axelrad et al. did identify that IBD patients on systemic chemotherapy did require more dose adjustments and time off from treatment. We are unable to extract this level of detail at the administrative data level and therefore cannot conclude whether this may be playing a role in the outcomes of Stage III patients. One of our questions was to know whether treatment in this population is less efficacious and we cannot determine this with the information that we have.

Similarly, with surgical treatment, we have not determined the rate of complete oncologic (R0) resection and the margins status, which is predictive of local recurrence. This is a factor that may impact outcomes and we cannot account for it. Additionally, there were many patients where tumor status, nodal status or grade were unknown. The amount of missing data was similar in both the IBD-associated and sporadic subgroups. In the multivariable analysis the 'unknown grade' group was associated with a worse prognosis. In some patients, we suspect if they had Stage IV disease, they never had resection but only a biopsy and full assessment of grade may not have been completed or documented. This would be an inherently worse prognosis group. However, this

difference remains significant in the multivariable analysis when stage is accounted for. The meaning of this is not clear.

Regarding surgical excision; another consideration is the expertise of the treating surgeon. Patients with IBD may have complex surgical histories and may be more often treated by colorectal, or surgical oncology trained surgeons; however, surgeon expertise and experience are not captured within the database. Additionally, surgeon metrics such as rate of positive margins, or local recurrence are not regularly collected or reported; thus we cannot use this information to determine if patients outcomes were influenced by the surgeon.

Additionally, having age presented as an ordinal variable, in order to protect patient privacy, limits our ability to investigate age specific risk. We split the age categories into equivalent age categories; however, the exact age at which the worse outcomes associated with IBD stop is unknown and would need age used as a continuous variable, which cannot be done within this database. Despite this we have identified important age-associated outcomes.

In this study, we have discussed colorectal cancer as a single entity and are not distinguishing between colon cancer and rectal cancer. The reason for this was primarily that the reported literature on IBD-associated cancer typically groups these diseases as one. Additionally, when we performed multivariable analysis the rectal location was not associated with a distinct difference in survival compared to other locations so for this purpose, we believe that keeping rectal cancer within the cohort is reasonable.

Within the study, we grouped all Stage IV patients together. However, in colorectal cancer, some Stage IV patients can be treated with curative intent, with resection of the primary tumor and metastatic disease. Within this study, we did not make distinction between Stage IV patients that have curative intent treatment with multiple surgeries and those that are treated with a more palliative approach. It is important to consider whether the presence of IBD would alter the likelihood that a patient receives more aggressive surgical management with resection of stage IV disease and if the oncologic outcomes in this group are similar to the sporadic CRC patients. A study by Hammoudi et al. identified that in patients with peritoneal metastases who are undergoing cytoreductive surgery and heated intra-peritoneal chemotherapy, patients with IBD-associated colon and small bowel cancers had worse overall and disease free survival.[84] Conversely with liver resection for colorectal metastases, a survival difference in IBD patients compared to patients without IBD has not been appreciated.[63] Technical factors including patients with IBD having multiple prior surgeries may act as a deterrent to very aggressive surgical treatment in the setting of unclear oncologic outcomes. We have identified that survival in Stage IV patients is not statistically different in the IBD-associated and sporadic CRC groups. However, future research is required to determine at a population level if patients with IBD are presenting with technically resectable metastatic disease at a similar rate as sporadic CRC patients and if they are approached with the same degree of aggressive surgical management. From our study, we identified that when stratified by age, patients with IBD-associated CRC were treated with chemotherapy, radiation and resection of the primary at similar rates to the sporadic CRC population. One hypothesis is that the same age-related approach is taken in the Stage IV setting and that IBD patients are treated similar to sporadic patients in the same age category; however, this is an area for future research.

Another limitation of administrative data is that staging is presented as the stage at diagnosis, and we do not have specific information about recurrence. One question is – in the early stage cancers, do we see increased recurrence rates in the IBD-associated CRC patients? Given that there are more T4 tumors, there may be a higher preponderance for peritoneal spread, or local recurrence. A retrospective study by Dugum et al. looked at 44 patients with IBD-associated CRC who received post-operative chemotherapy and compared their recurrence and survival outcomes to 176 propensity score matched controls with sporadic CRC. They were unable to identify a significant difference in disease free survival (HR 0.60; 95% CI 0.35–1.05; P=0.074) or overall survival ((HR=0.87; 95% CI 0.54–1.4; P=0.58).[50] However, this study was in those that received adjuvant therapy; and does not address the recurrence risk in those who would not typically receive chemotherapy after surgery. Specifically, are Stage I and II tumors in the IBD population more likely to recur? Administrative data limits our ability to determine recurrence, but this will be an important point of future prospective research because if the early cancers in the IBD population do in fact have increased recurrence rates, the criteria for surveillance and adjuvant therapy may be expanded for IBD-associated CRC patients with early stage tumors.

In the same vein- many oncology studies describe outcomes including disease free survival, or cancer specific survival. Because we do not have the capability to identify recurrence or specific cause of death these oncologic survival descriptors cannot be used. This limits the ability to compare these results to other studies.

Conclusions

We have identified that patients with IBD-associated CRC present at similar stages to patients with sporadic CRC but exhibit some pathologic features that may portend worse prognosis such as T4, N2-3 and high grade disease. Patients with IBD had similar rates of surgery and radiation, and higher rates of chemotherapy use, which is a reflection of their younger age at diagnosis. When looking at the whole population of patients, survival outcomes appear similar between the groups. However, young patients (<65) with IBD-associated CRC have worse survival outcomes than young (<65) patients with sporadic CRC. This difference is no longer apparent in patients over 65. These findings inform prognostication and may direct future research on treatment for this high-risk population.

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Table 1. Baseline patient demographics, treatments and survival outcomes in Sporadic and IBD-Associated CRC

Demographic	Sporadic CRC N=66,354	IBD-Associated CRC N=783	p-value
Sex, N Male (%)	36,264 (54.7)	460 (58.8)	0.022
Age (median range)	70-74	55-59	<0.001
Primary tumor location*, N (%)			
Right Sided	25250 (38.1)	301 (38.4)	p=0.43**
Left Sided	23420 (35.3)	224 (28.6)	
Rectum	15670 (23.6)	215 (27.5)	p=0.003
Unknown	2014 (3.0)	43 (5.5)	
Tumor Category, N (%)			
T0/1	8,628 (13.0)	99 (12.6)	<0.001***
T2	7,081 (10.7)	80 (10.2)	
T3	21,671 (32.7)	213 (27.2)	
T4	8,775 (13.2)	144 (18.4)	
Unknown	20,199 (30.4)	247 (31.5)	
Nodal status, N (%)			
N0	28,410 (42.8)	321 (41.0)	0.029***
N1	12,687 (19.1)	131 (16.7)	
N2-3	6,342 (9.6)	95 (12.1)	
Unknown	18,915 (28.5)	236 (30.1)	
Stage, N (%)			
1	13,855 (20.9)	160 (20.4)	0.65
2	15,961 (24.1)	197 (25.2)	
3	17,227 (26.0)	194 (24.8)	
4	11,310 (17.0)	128 (16.4)	
Unknown	8,001 (12.1)	104 (13.3)	
Grade, N (%)			
1	2,135 (4.2)	27 (4.6)	<0.001
2	33,217 (64.9)	308 (52.1)	
3	2,470 (4.8)	69 (11.7)	
4	3,114 (6.1)	69 (11.7)	
Unknown	10,219 (20.0)	118 (20.0)	
IBD type, N (%)	N/A	783	
Crohn's Disease		293 (37.4)	
Ulcerative Colitis		470 (60.0)	
Unclassified		20 (2.6)	
Treatment, N (%)			
Chemotherapy	26,644 (40.2)	379 (48.4)	<0.001
Resective Surgery	51,187 (77.1)	621 (79.3)	0.15
Non-Resective Surgery	1,585 (2.4)	31 (4.0)	0.004
Radiotherapy	14,676 (22.1)	179 (22.9)	0.62

No Treatment	8,647 (13.0)	64 (8.2)	<0.001
Post-Operative Mortality**** %, (95% CI)	2.9 (2.7-3.1)	2.7 (1.6-4.7)	0.31
Charlson Comorbidity Index (median)	4	4	0.27
Income Quintile, N (%)			
1	12,641 (19.1)	117 (15.0)	<0.001
2	13,708 (20.8)	139 (17.8)	
3	13,251 (20.1)	158 (20.2)	
4	13,447 (20.4)	189 (24.2)	
5	13,020 (19.7)	178 (22.8)	
Overall Survival (OS)			p=0.86
N (%) Deaths	36245 (54.6)	425 (54.3)	
Median (months)(95% CI)	67.2 (65.9-68.7)	70.7 (55.3-84.3)	
5-year OS (%)(95% CI)	52.6 (52.2-53.0)	52.5 (48.5-56.3)	

*Right sided is defined from cecum up to, but not including, the splenic flexure; left sided is defined as splenic flexure to rectosigmoid, inclusive. Tumor location is known in 97% of the patient population. Patients with tumors categorized as C18.8 (overlapping lesion of the colon) and C18.9 (Colon NOS) were grouped together as Unknown due to small numbers.

**Analysis of right versus left sided tumors includes the rectum on the left side. When the rectum was not included, the p-value is 0.013.

***p-values reflect differences in those with known T or N stage

****Mortality rate within 30 days of resective surgery- restricted to Stage I, II and III patients

Table 2. Regression models for prognostic factors of overall survival

Factor (Unit)	Hazard Ratio (95% CI) *	Hazard Ratio (95% CI)*
	Univariate Model	**Multivariable Model**
IBD at Diagnosis (Yes vs No)	1.01 (0.91, 1.13) p=0.80	1.45 (1.29, 1.63)
Age (/group)**	1.22 (1.22, 1.23)	1.23 (1.22, 1.24)
Stage		
1	Reference	Reference
2	1.55 (1.49, 1.62)	1.44 (1.37, 1.51)
3	2.02 (1.94, 2.10)	1.64 (1.57, 1.73)
4	9.55 (9.18, 9.94)	6.20 (5.90, 6.51)
Unknown	3.33 (3.18, 3.48)	2.93 (2.77, 3.10)
Tumor Grade		
1		
2	Reference	Reference
3	1.28 (1.18, 1.37)	0.94 (0.88, 1.02)
4	2.61 (2.39, 2.84)	1.48 (1.35, 1.62)
Unknown	2.41 (2.21, 2.63)	1.34 (1.23, 1.47)
	1.98 (1.84, 2.13)	1.74 (1.61, 1.88)
Sex (Female vs Male)	1.00 (0.98, 1.02) p=0.82	0.98 (0.95, 1.01) p=0.11
Income Quintile (/quintile)	0.94 (0.93, 0.95)	0.96 (0.95, 0.97)
Charlson Score (/unit)	1.26 (1.25, 1.26)	1.18 (1.17, 1.18)
Rio Score (/unit)	1.16 (1.10, 1.24)	1.001 (1.000, 1.001) p=0.047
Year of CRC Diagnosis (/year)	0.99 (0.99, 1.00) P=0.002	1.11 (1.11, 1.12)
ICD-0-3 Code***		
C18.0		
C18.2	1.29 (1.25, 1.34)	1.04 (0.99, 1.09)
C18.3	1.11 (1.07, 1.16)	0.98 (0.93, 1.03)
C18.4	1.27 (1.19, 1.35)	1.06 (0.99, 1.14)
C18.5	1.28 (1.21, 1.35)	1.08 (1.02, 1.15)
C18.6	1.23 (1.13, 1.33)	1.07 (0.98, 1.17)
C18.7	1.01 (0.95, 1.08)	0.97 (0.90, 1.04)
C18.8	0.98 (0.95, 1.02)	0.95 (0.91, 0.99)
C18.9	2.08 (1.60, 2.72)	1.23 (0.89, 1.68)
C19	3.95 (3.74, 4.17)	1.85 (1.72, 1.99)
C20	1.06 (1.02, 1.11)	0.93 (0.88, 0.98)
	Reference	Reference
Known Location of Metastases		

Bone		
Lung	4.43 (4.01, 4.89)	1.25 (1.13, 1.39)
Liver	4.34 (4.13, 4.56)	1.15 (1.09, 1.21)
Brain	4.43 (4.30, 4.57)	1.19 (1.15, 1.24)
	6.15 (5.16, 7.31)	1.70 (1.42, 2.03)

*p-value for each Hazard Ratio is <0.001 unless otherwise specified

**Age group is broken down into categories as specified in methods.

***ICD 0-3 Codes: C18.0:Cecum; C18.2:Ascending colon; C18.3:Hepatic flexure of colon; C18.4: Transverse colon; C18.5: Splenic flexure of colon; C18.6: Descending colon; C18.7:Sigmoid colon; C18.8:Overlapping lesion of colon; C18.9: Colon, NOS;C19: Rectosigmoid junction; C20: Rectum, NOS

Table 3. Treatment received, and survival outcomes broken down by age

		Sporadic CRC	IBD-Associated CRC	p-value
% (n/N) Resective Surgery				
Age Groups	18-49	77.3 (3684/4766)	75.2 (151/201)	0.47
	50-64	78.9 (14210/18012)	82.9 (237/286)	0.10
	65-79	80.6 (21989/27299)	80.0 (160/200)	0.85
	80+	69.5 (11304/16277)	76.0 (73/96)	0.16
% (n/N) with Chemotherapy				
Age Groups	18-49	65.3 (3111/4766)	66.2 (133/201)	0.79
	50-64	56.1 (10098/18012)	54.9 (157/286)	0.69
	65-79	41.2 (11258/27299)	40.5 (81/200)	0.83
	80+	13.4 (2177/16277)	8.3 (8/96)	0.15
% (n/N) with Radiotherapy				
Age Groups	18-49	30.9 (1474/4766)	25.9 (52/201)	0.13
	50-64	28.0 (5049/18012)	27.6 (79/286)	0.88
	65-79	21.8 (5959/27299)	17.5 (35/200)	0.14
	80+	13.5 (2194/16277)	13.5 (13/96)	0.99
5-year OS, % (95% CI)				
Age Groups	18-49	71.4 (70.0-72.7)	56.8 (49.4-63.5)	<0.001
	50-64	69.6 (68.9-70.4)	61.8 (55.6-67.4)	<0.001
	65-79	59.5 (58.9-60.1)	59.0 (51.4-65.9)	0.71
	80+	34.6 (33.8-35.4)	33.9 (24.4-43.6)	0.78

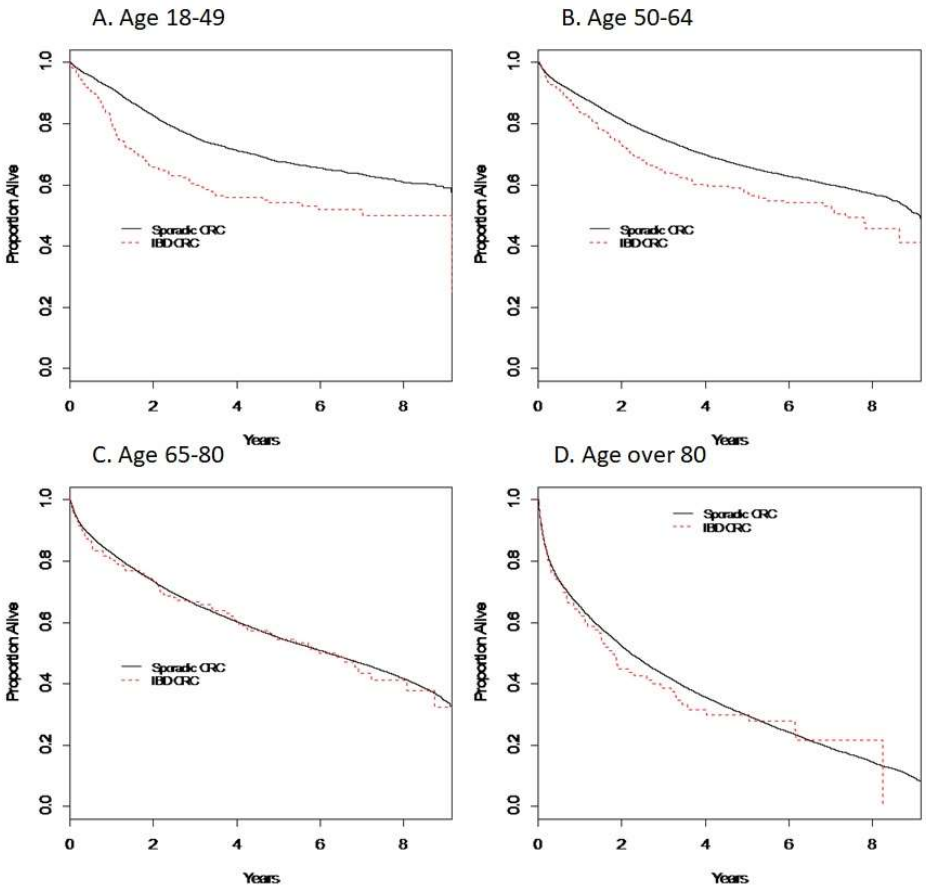


Figure 1 A-D. Survival by IBD status for different age groups. A) Age 18-49, B) Age 50-64, C) Age 65-80, D) Age over 80. Black line represents patients with sporadic CRC, dotted red line represents patients with IBD-associated CRC.

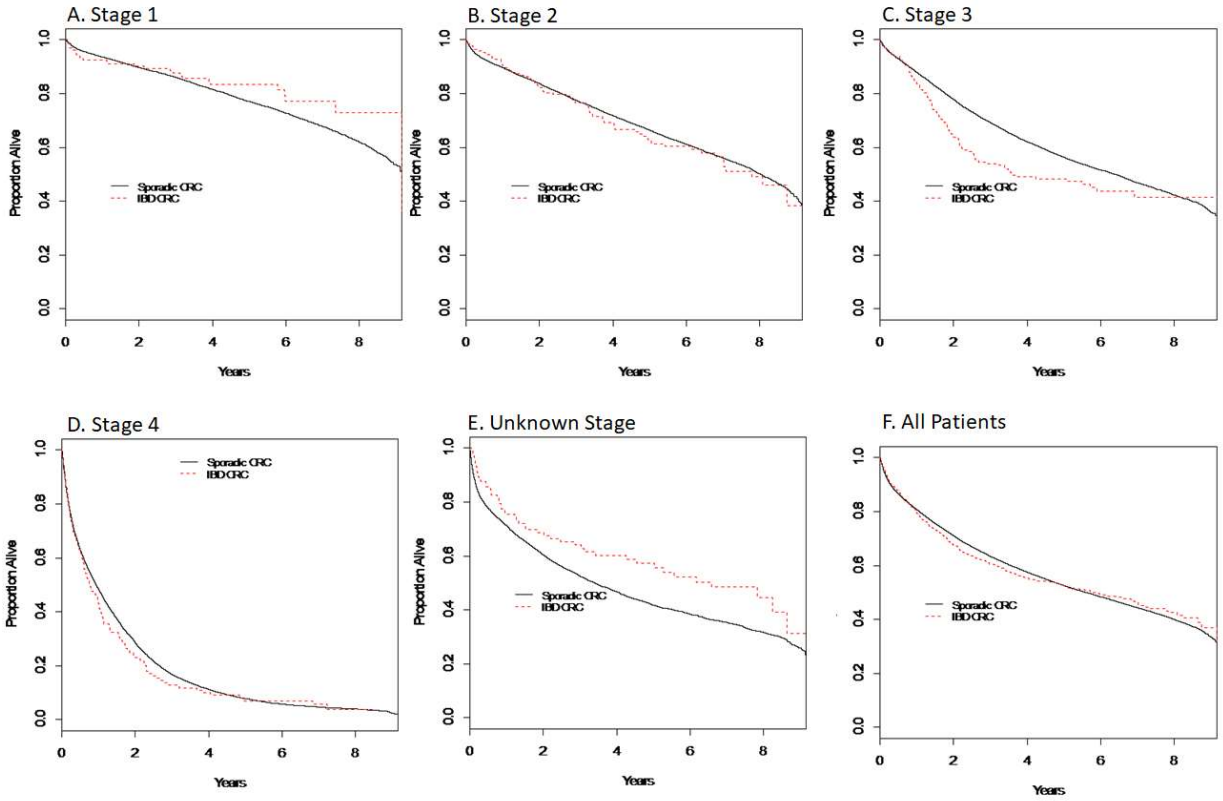


Figure 2 (A-F) Survival by IBD status for different stage groups: A) Stage 1, B) Stage 2, C) Stage 3, D) Stage 4, E) Stage Unknown, F) All Stages. Black line represents patients with sporadic CRC, dotted red line represents patients with IBD-associated CRC.

Table 4. Hazard Ratio for death with IBD associated colorectal cancer, compared to sporadic colorectal
cancer, broken down by age and stage*

Age Groups	Stage Groups	N with sporadic / IBD associated CRC	HR (95% CI)	p-value
Age 18-49	Stage I	816 / 33	3.1 (1.2-7.0)	0.016
	Stage II	870 / 46	3.3 (1.9-5.9)	<0.001
	Stage III	1460 / 46	1.9 (1.1-3.1)	0.015
	Stage IV	957 / 49	1.8 (1.4-2.5)	<0.001
	Unknown Stage	663 / 27	1.4 (0.7-2.6)	0.38
Age 50-64	Stage I	4025 / 66	0.6 (0.2-1.8)	0.33
	Stage II	3646 / 60	2.2 (1.5-3.5)	<0.001
	Stage III	5026 / 81	2.0 (1.5-2.8)	<0.001
	Stage IV	3277 / 39	1.5 (1.1-2.1)	0.017
	Unknown Stage	2038 / 40	1.6 (1.0-2.5)	0.042
Age 65-79	Stage I	6130 / 42	1.3 (0.7-2.3)	0.42
	Stage II	6904 / 63	1.1 (0.7-1.7)	0.66
	Stage III	6997 / 43	1.5 (0.99-2.3)	0.054
	Stage IV	4430 / 29	0.9 (0.6-1.3)	0.62
	Unknown Stage	2838 / 23	0.6 (0.3-1.2)	0.13
Age 80+	Stage I	2884 / 19	0.9 (0.4-1.7)	0.67
	Stage II	4541 / 28	1.1 (0.7-1.8)	0.75
	Stage III	3744 / 24	1.5 (0.98-2.4)	0.059
	Stage IV	2646 / 11	1.1 (0.6-2.1)	0.68
	Unknown Stage	2462 / 14	0.9 (0.5-1.7)	0.84

*Hazard Ratios are not adjusted for other factors due to the large number of variables leading to small sizes and losing significance. The adjusted analysis did identify a similar trend.

Table 5. Treatments received broken down by stage

Treatment:	Stage	Sporadic CRC	IBD-CRC	p-value
Denominator N	I	13855	160	
	II	15961	197	
	III	17227	194	
	IV	11310	128	
	Unknown	8001	104	
Chemotherapy N (%)	I	1609 (11.6%)	27 (16.9)	0.039
	II	4552 (28.5)	82 (41.6)	<0.001
	III	11694 (67.9)	148 (76.3)	0.013
	IV	6524 (57.7)	87 (68.0)	0.019
	Unknown	2265 (28.3)	35 (33.7)	0.23
Resective Surgery N (%)	I	10983 (79.3)	140 (87.5)	0.011
	II	14984 (93.9)	185 (93.9)	0.99
	III	16150 (93.8)	178 (91.8)	0.25
	IV	5396 (47.7)	55 (43.0)	0.29
	Unknown	3674 (45.9)	63 (60.6)	0.003
Radiotherapy N (%)	I	1633 (11.8)	19 (11.9)	0.97
	II	3405 (21.3)	53 (26.9)	0.058
	III	5520 (32.0)	59 (30.4)	0.63
	IV	2701 (23.9)	29 (22.7)	0.75
	Unknown	1417 (17.7)	19 (18.3)	0.88

Table 6. Five year survival for Stage 3 patients, according to IBD status and whether they received adjuvant chemotherapy (%, 95% CI)

	Received Chemotherapy	Did not receive Chemotherapy
Sporadic CRC	70.7 (69.6-71.5)	41.2 (39.8-42.6)
IBD-associated CRC	57.9 (49.1-65.7)	34.8 (21.5-48.4)

Table 7. Baseline patient demographics, treatments and survival outcomes in Sporadic and IBD-Associated CRC, Restricted to Stage I, II and III patients who underwent resective surgery

Demographic	Sporadic CRC N=40635	IBD-Associated CRC N=475	p-value
Sex, N Male (%)	22055 (54.3)	272 (57.3)	0.19
Age (median range)	70-74	60-64	<0.001
Primary tumor location*, N (%)			
Right Sided	17566(43.2)	222 (46.7)	p=0.07**
Left Sided	14600 (35.9)	143 (30.1)	
Rectum	8320 (20.5)	102 (21.5)	p=0.49
Unknown	149 (0.004)	8 (1.7)	
Stage, N (%)			
1	10543 (26.0)	135 (28.4)	0.21
2	14536 (35.8)	168 (35.4)	
3	15556 (38.3)	172 (36.2)	
IBD type, N (%)	N/A		
Crohn's Disease		171 (36.0)	
Ulcerative Colitis		291 (61.3)	
Unclassified		13 (2.7)	
Treatment, N (%)			
Chemotherapy	15927 (39.2)	216 (45.5)	0.005
Radiotherapy	8396 (20.7)	92 (19.4)	0.49
Charlson Comorbidity Index (median)	3	3	0.52
Overall Survival (OS)			
N (%) Deaths	27852 (68.5)	156 (67.2)	0.21
Median (months)(95% CI)	101.5 (100.3, 103.3)	110.0 (96.9, NR)	
5-year OS (%)(95% CI)	68.5 (67.9, 69.0)	65.0 (59.9, 69.7)	

*Right sided is defined from cecum up to, but not including, the splenic flexure; left sided is defined as splenic flexure to rectosigmoid, inclusive.

**p-value reflects right sided versus left sided tumors with rectal tumors being included in left sided tumors. If they are excluded, p=0.018.

Table 8. Survival outcomes, and treatment received broken down by age, limited to Stage I, II and III patients who underwent resective surgery.

		Sporadic CRC	IBD-associated CRC	p-value
N (%) with Chemotherapy				
Age Groups	18-49	1801/2732 (65.9)	68/102 (66.7)	0.88
	50-64	6025/10991 (54.8)	100/179 (55.9)	0.78
	65-79	6882/17567 (39.2)	43/129 (33.3)	0.18
	80+	1219/9345 (13.0)	Small #	0.20
N (%) with Radiotherapy				
Age Groups	18-49	863/2732 (31.6)	28/102 (27.5)	0.38
	50-64	2988/10991 (27.2)	39/179 (21.8)	0.11
	65-79	3560/17567 (20.3)	19/129 (14.7)	0.12
	80+	985/9345 (10.5)	6/65 (9.2)	0.73
5-year OS % (95% CI)				
Age Groups	18-49	85.5 (83.9, 87.0)	75.4 (64.4, 83.4)	0.005
	50-64	82.6 (81.7, 83.4)	71.1 (62.7, 77.9)	<0.001
	65-79	70.1 (69.3, 70.9)	63.2 (52.6, 72.1)	0.063
	80+	44.0 (42.8, 45.2)	36.6 (23.9, 49.3)	0.074

Table 9. Regression models for prognostic factors of overall survival for patients with Stage I, II and III CRC who underwent resective surgery

Factor (Unit)	Hazard Ratio (95% CI) *	Hazard Ratio (95% CI)*
	Univariate Model	**Multivariable Model**
IBD at Diagnosis (Yes vs No)	1.11 (0.95, 1.30) p=0.21	1.59 (1.33, 1.89)
Age (/group)**	1.32 (1.31, 1.33)	1.30 (1.29, 1.32)
Stage		
1	Reference	Reference
2	1.69 (1.61, 1.78)	1.44 (1.36, 1.52)
3	2.33 (2.22, 2.45)	1.56 (1.47, 1.65)
Tumor Grade		
1	Reference	Reference
2	1.53 (1.37, 1.70)	1.04 (0.93, 1.16)
3	2.25 (1.97, 2.56)	1.40 (1.22, 1.59)
4	3.11 (2.75, 3.53)	1.51 (1.33, 1.72)
Unknown	1.45 (1.28, 1.64)	1.30 (1.15, 1.47)
Sex (Female vs Male)	0.94 (0.91, 0.97)	0.87 (0.84, 0.91)
Income Quintile (/quintile)	0.93 (0.92, 0.94)	0.96 (0.95, 0.98)
Charlson Score (/unit)	1.27 (1.27, 1.28)	1.24 (1.23, 1.25)
Rio Score (/unit)	1.23 (1.12, 1.34)	1.002 (1.001, 1.003)
Year of CRC Diagnosis (/year)	1.14 (1.13, 1.15)	1.20 (1.19, 1.21)
ICD-0-3 Code***		
C18.0	1.42 (1.35, 1.50)	1.03 (0.96, 1.10)
C18.2	1.30 (1.22, 1.37)	0.93 (0.87, 1.00)
C18.3	1.23 (1.12, 1.36)	0.96 (0.86, 1.08)
C18.4	1.49 (1.38, 1.61)	1.06 (0.97, 1.16)
C18.5	1.43 (1.28, 1.61)	1.17 (1.02, 1.34)
C18.6	1.15 (1.05, 1.25)	1.01 (0.91, 1.12)

C18.7	1.03 (0.98, 1.09)	1.00 (0.93, 1.07)
C18.8	1.33 (0.77, 2.30)	1.14 (0.63, 2.06)
C18.9	1.51 (1.13, 2.01)	2.03 (1.49, 2.75)
C19	0.99 (0.92, 1.06)	0.89 (0.82, 0.97)
C20	Reference	Reference

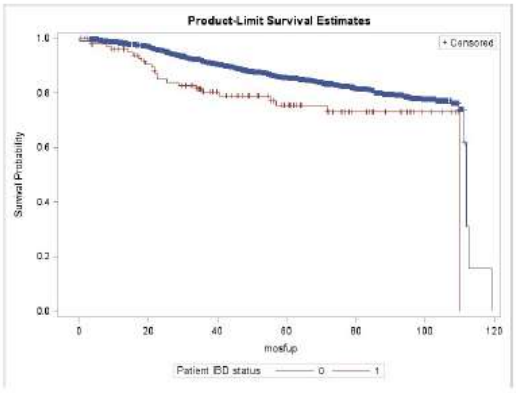
*p-value for each Hazard Ratio is <0.001 unless otherwise specified

**Age group is broken down into categories as specified in methods.

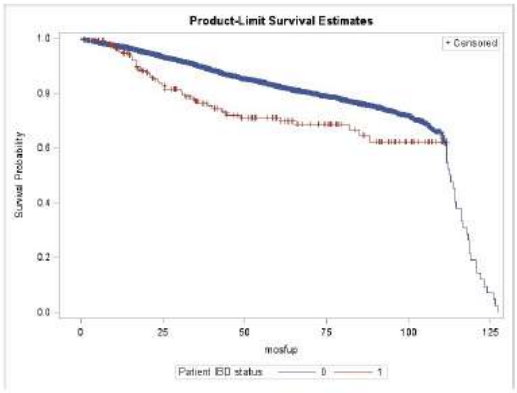
***ICD 0-3 Codes: C18.0:Cecum; C18.2:Ascending colon; C18.3:Hepatic flexure of colon; C18.4: Transverse colon; C18.5: Splenic flexure of colon; C18.6: Descending colon; C18.7:Sigmoid colon; C18.8:Overlapping lesion of colon; C18.9: Colon, NOS;C19: Rectosigmoid junction; C20: Rectum, NOS

Figure 3. Survival by IBD status for different age groups, limited to Stage I, II and III patients who underwent resective surgery

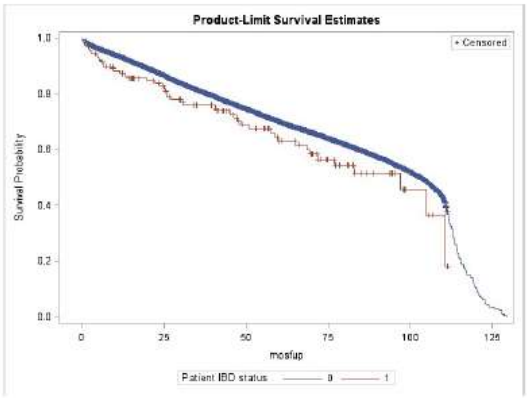
a) Age <49



b) Age 50-64



c) Age 65-79



d) Age 80+

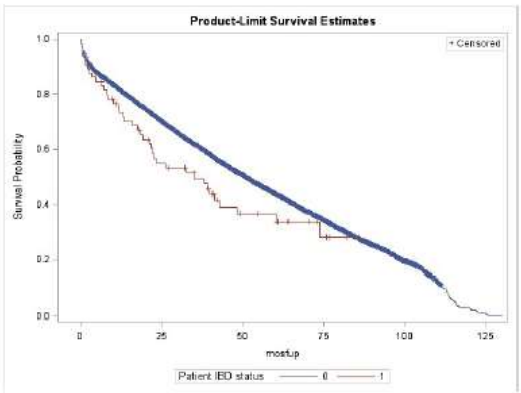


Table 10. Baseline characteristics, treatment and outcomes for IBD patients, broken down by IBD subtype *

Demographic	Crohn's Disease (N=293)	Ulcerative Colitis (N= 470)	p-value
Sex, N Male (%)	158 (53.9)	288 (61.3)	0.045
Age (median range)	55-59	60-64	0.023
Primary tumor location**, N (%)			
Right Sided	107 (36.5)	184 (39.1)	0.69
Left Sided	90 (30.7)	144 (30.6)	
Rectum	88 (30.0)	124 (26.4)	0.31
Unknown	8 (2.7)	18 (3.8)	
Tumor Category, N (%)			0.92
T0-T1	37 (12.6)	61 (13.0)	
T2	29 (9.9)	49 (10.4)	
T3	79 (27.0)	130 (27.7)	
T4	54 (18.4)	86 (18.3)	
Unknown	94 (32.1)	144 (30.6)	
Node positive, N (%)***	73 (37.1)	149 (44.0)	0.12
Stage, N (%)			0.58
I	57 (19.5)	98 (20.9)	
II	81 (27.7)	111 (23.6)	
III	69 (23.6)	120 (25.5)	
IV	44 (15.0)	80 (17.0)	
Unknown	42 (14.3)	61 (13.0)	
Grade, N (%)			0.66
1	11 (5.1)	16 (4.3)	
2	107 (49.5)	193 (52.3)	
3	22 (10.2)	46 (12.5)	
4	24 (11.1)	43 (11.7)	
Unknown	52 (24.1)	71 (19.2)	
Treatment, N (%)			
Chemotherapy	151 (51.5)	222 (47.2)	0.26
Resective Surgery	225 (76.8)	379 (80.6)	0.23
Non-Resective Surgery	15 (5.1)	16 (3.4)	0.26
Radiotherapy	84 (28.7)	90 (19.2)	0.003
No Treatment	28 (9.6)	33 (7.0)	0.22
Charlson Comorbidity Index median, (range)	2 (0-9)	2 (0-10)	0.15
Income Quintile, N (%)			
1	42 (14.4)	73 (15.6)	0.82
2	54 (18.5)	81 (17.3)	
3	54 (18.5)	98 (20.9)	

4 5	77 (26.4) 65 (22.3)	107 (22.8) 110 (23.5)	
Overall Survival (OS) N (%) Deaths Median (months)(95% CI) 5-year OS (%)(95% CI)	 143 (51.2) 61.2 (44.1, 86.8) 50.6 (44.4, 56.5)	 273 (41.9) 123.1 (94.0, NR) 59.9 (55.1, 64.4)	 0.017

*Unclassified subtype not included as numbers too small to report

Table 11. Breakdown of Costing for IBD-Associated and Sporadic CRC patients in first two years from diagnosis of colorectal cancer.

	Sporadic CRC Median in CAD (Maximum)	**IBD-associated CRC Median in CAD (Maximum)**	**p-value**
N	66354	783	
Inpatient	$25149 ($4,325,495)	$33591 ($1,787,195)	<0.001
Outpatient	$4293 ($169,429)	$5801 ($54074)	<0.001
Same Day Surgery	$1406 ($68273)	$1482 ($24593)	0.17
NACRS Emergency Department	$760 ($74901)	$1072 ($21336)	<0.001
NACRS Dialysis	$0 ($357511)	$0 ($247827)	0.77
NACRS Cancer	$0 ($430562)	$785 ($162599)	0.013
Ontario Drug Benefit	$1645 ($332036)	$1406 ($113846)	0.011
Complex Continuing Care	$0 ($804851)	$0 ($251385)	0.007
OHIP and ODB LTC	$0 ($109744)	$0 ($17788)	0.020
Continuing Care Reporting System, LTC	$0 ($212016)	$0 ($123461)	0.053
LTC	$0 ($212016)	$0 ($123461)	0.016
Fee for service OHIP	$11385 ($278446)	$13258 ($192725)	<0.001
SB HFOFHTN OHIP	$0 ($3096)	$0 ($834)	0.009
Other OHIP	$0 ($27606)	$56 ($15275)	<0.001
EDAFA OHIP	$0 ($3923)	$0 ($582)	0.006
Medical Oncology OHIP	$0 ($72397)	$115 ($31620)	<0.001
Radiation Oncology OHIP	$0 ($5970)	$0 ($2974)	0.61
STD PAY OHIP	$12886 ($214534)	$15021 ($191531)	<0.001
Lab OHIP	$233 (11072)	$264 ($5069)	0.023
Non-physician OHIP	$0 ($8127)	$0 ($1664)	<0.001
OMHRS	$0 ($808009)	$0 ($22594)	0.37
TOTAL COSTS	$46293 ($2,684,077)	$53256 ($1,332,992)	<0.001

NACRS: National Ambulatory Care Reporting System
LTC: Long term care
OHIP: Ontario Health Insurance Plan
ODB: Ontario Drug Benefit
SB HFOFHTN: OHIP Family Health Organization or Family Health Network Shadow Billings
EDAFA: Emergency Department Alternative Funding Agreement
STD PAY OHIP: OHIP all billings- using an annual average cost
OMHRS: Ontario Mental Health Reporting System

Table 12a. Cost analyses for all patients in the first 10 years from time of diagnosis of CRC

		Sporadic CRC	IBD associated CRC	p-value*
N		48963	574	
Cost in Year 1	Median (Max)	$39090 ($1,890,058)	$47270 ($671,762)	<0.001
Costs to Year 2	Median (Max)	$46780 ($2,684,077)	$56651 ($1,332,992)	<0.001
Costs to Year 5	Median (Max)	$58364 ($2,684,077)	$69722 ($1,332,992)	<0.001
Costs to Year 10	Median (Max)	$62233 ($2,684,077)	$74822 ($1,332,992)	<0.001

* Not a formal economic analysis – just a simple Wilcoxon rank sum test

Table 12b. Cost analyses for all patients in the first 10 years from time of diagnosis of CRC-excluding patients with a diagnosis of rectal cancer

		Sporadic CRC	IBD associated CRC	p-value*
N		39338	452	
Cost in Year 1	Median (Max)	$35452 ($1,890,058)	$42471 ($671,762)	<0.001
Costs to Year 2	Median (Max)	$42498 ($2,684,077)	$51009 ($1,332,992)	<0.001
Costs to Year 5	Median (Max)	$53545 ($2,684,077)	$62549 ($1,332,992)	<0.001
Costs to Year 10	Median (Max)	$57234 ($2,684,077)	$68720 ($1,332,992)	<0.001

* Not a formal economic analysis – just a simple Wilcoxon rank sum test

Table 13a. Cost analyses in patients with Stage I, II and III who undergo resective surgery

		Sporadic CRC	IBD associated CRC	p-value*
N		40635	475	
Cost in Year 1	Median (Max)	$36794 ($1,890,058)	$44769 ($671,762)	<0.001
Costs to Year 2	Median (Max)	$44155 ($2,684,077)	$54451 ($1,332,992)	<0.001
Costs to Year 5	Median (Max)	$55798 ($2,684,077)	$66295 ($1,332,992)	<0.001
Costs to Year 10	Median (Max)	$59806 ($2,684,077)	$72518 ($1,332,992)	<0.001

* Not a formal economic analysis – just a simple Wilcoxon rank sum test

Table 13b. Cost analyses in patients with Stage I, II and III who undergo resective surgery- with rectal cancer patients excluded

		Sporadic CRC	IBD associated CRC	p-value*
N		32315	373	
Cost in Year 1	Median (Max)	$32845 ($1,890,058)	$40509 ($671,762)	<0.001
Costs to Year 2	Median (Max)	$39707 ($2,684,077)	$49398 ($1,332,992)	<0.001
Costs to Year 5	Median (Max)	$50735 ($2,684,077)	$59254 ($1,332,992)	<0.001
Costs to Year 10	Median (Max)	$54490 ($2,684,077)	$65712 ($1,332,992)	<0.001

* Not a formal economic analysis – just a simple Wilcoxon rank sum test

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