EDITOR'S CHOICE

High frequency of early colorectal cancer in inflammatory bowel disease

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ABSTRACT

Background and aim: To detect precancerous dysplasia or asymptomatic cancer, patients suffering from inflammatory bowel disease often undergo colonoscopic surveillance based on American or British guidelines. It is recommended that surveillance is initiated after 8–10 years of extensive colitis, or after 15–20 years for left-sided disease. These starting points, however, are not based on solid scientific evidence. Our aim was to assess the time interval between onset of inflammatory bowel disease (IBD) and colorectal carcinoma (CRC), and subsequently evaluate how many patients developed cancer before their surveillance was recommended to commence.

Methods: A nationwide automated pathology database (PALGA) was consulted to identify patients with IBD-associated colorectal carcinoma in seven university medical centres in The Netherlands between January 1990 and June 2006. Data were collected retrospectively from patient charts. Time intervals between onset of disease and cancer diagnosis were calculated in months.

Results: 149 patients were identified with confirmed diagnoses of IBD and CRC (ulcerative colitis n = 89/ Crohn's disease n = 59/indeterminate colitis n = 1). Taking *date of diagnosis* as the entry point, 22% of patients developed cancer before the 8 or 15 year starting points of surveillance, and 28% if surveillance was commenced 10 or 20 years after diagnosis for extensive or left-sided disease, respectively. Using *onset of symptoms* to calculate the time interval, 17–22% of patients would present with cancer prior to the surveillance starting points.

Conclusions: These results show that the diagnosis of colorectal cancer is delayed or missed in a substantial number of patients (17–28%) when conducting surveillance strictly according to formal guidelines.

Patients with inflammatory bowel disease (IBD) are at increased risk of developing colorectal cancer (CRC). Eaden *et al*[1] showed cumulative risks of 2%, 8% and 18% after 10, 20 and 30 years of disease, respectively, for patients with ulcerative colitis. Jess *et al*[2] found an increased standardised incidence ratio of 1.9 for CRC in Crohn's disease. Although IBD-associated CRC only constitutes 1–2% of all colorectal carcinomas, it is a frequent cause of death in IBD patients.[1]

IBD-associated colorectal carcinogenesis is characterised by an "inflammation–dysplasia–carcinoma" sequence[3] which differs from the "adenoma–carcinoma" sequence in sporadic CRC. High-grade or multifocal low-grade dysplasia indicate that the entire mucosal lining of the colon, exposed to chronic inflammation, is at increased risk of developing cancer,[3 4] thereby heralding the rigorous advice of proctocolectomy. In order to prevent development of CRC, IBD patients are advised to undergo colonic surveillance aimed at detection of dysplasia or asymptomatic early CRC at a surgically curable stage. Currently, the surveillance guidelines followed most often are those defined by the American Gastroenterological Association (AGA)[5] and the British Society for Gastroenterology (BSG).[6]

These guidelines recommend commencing surveillance after 8–10 years of disease in cases of Crohn's disease or extensive ulcerative colitis, and after 15–20 years of disease in cases of left-sided ulcerative colitis. Starting surveillance before these time intervals is not recommended. The evidence on which this is based is poor, however. The aim of the present study was to assess the time intervals between the occurrence of IBD and CRC and to evaluate how often IBD-associated CRC occurred before the first surveillance colonoscopy is advised.

MATERIALS AND METHODS

Study population

PALGA, the nationwide network and registry of histo- and cytopathology[7] containing pathology reports generated in The Netherlands dating back to 1971, was used to search for patients with IBD-associated CRC. These reports are concluded with diagnostic terms in line with SNOMED terminology. The PALGA database has had complete nationwide coverage since 1990. Therefore a PALGA search for the time period of January 1990 until June 2006 in all Dutch university medical centres for synchronous or metachronous diagnoses of IBD and CRC was performed. The following combinations of search terms were used: ulcerative colitis AND adenocarcinoma, Crohn's disease AND adenocarcinoma, colon AND colitis AND adenocarcinoma, colon AND inflammation AND adenocarcinoma, colon AND chronic inflammation AND adenocarcinoma, colon AND idiopathic colitis AND adenocarcinoma, colon AND adenocarcinoma AND active inflammation.

Data collection

The following data were collected from patient charts: type of IBD, sex, age at diagnosis of IBD, age at diagnosis of CRC, date of diagnosis of IBD, date of onset of symptoms attributable to IBD, date of diagnosis of CRC, maximum extent of disease as seen on colonoscopy, maximum

Box 1 British Society of Gastroenterology guidelines

1. Surveillance colonoscopies should be performed when the disease is in remission
2. All patients should have a screening colonoscopy after 8–10 years which will also clarify disease extent
3. Regular surveillance should begin after 8–10 years (from onset of symptoms) for pancolitis and after 15–20 years for left-sided disease
4. As the risk of cancer increases exponentially with time, there should be a decrease in the screening interval with increasing disease duration. For patients with pancolitis, a colonoscopy should be conducted every 3 years in the second decade of disease, every 2 years in the third decade, and yearly by the fourth decade of disease
5. Specimens from two to four random biopsies every 10 cm from the entire colon should be taken with additional samples of suspicious areas
6. Patients with primary sclerosing cholangitis (including those with an orthotropic liver transplant) represent a subgroup at higher risk of cancer and they should have annual colonoscopy

histological extent of disease, tumour location, tumour stage, history of colonic surgery or surgery during follow-up, history of 5-aminosalicylic acid (5-ASA) medication, concomitant primary sclerosing cholangitis (PSC). Charts were additionally scrutinised on whether or not patients had undergone surveillance colonoscopies based on formal guideline protocols[5 6] prior to diagnosis of CRC.

AGA and BSG colonic surveillance guidelines for patients with IBD

The differences between the AGA and BSG guidelines (box 1) are small. In the British guidelines shorter colonoscopy intervals are recommended with every subsequent decade of disease, while in the American guidelines colonoscopy is advised every 1–2 years with no increment in frequency for longer disease duration. Initiation of surveillance after 15 years of left-sided colitis instead of 15–20 years is another small difference between the AGA and BSG guidelines, respectively.

Statistical analysis

As the entry point of follow-up the date of diagnosis of IBD as well as the date of onset of symptoms attributable to IBD were analysed separately. Intervals between these starting points and the date of diagnosing CRC were measured in months. From these data, calculations were made of the percentages of patients who developed CRC before 8 or 15 years of disease duration for extensive or left-sided colitis, respectively, or before 10 or 20 years of disease duration for extensive or left-sided colitis, respectively. Intervals of patients with Crohn's colitis were only compared with the 8 and 10 year intervals as there is no explicit distinction for extent of disease in the AGA and BSG guidelines for these patients. A similar approach was chosen for patients with unknown disease extent. Statistical analysis was done with SPSS for Windows software version 12.0.1.

RESULTS

Patients

Our search resulted in 166 patients, of which 17 were excluded, leaving 149 patients with IBD-associated CRC for analysis (table 1). The reasons for exclusion were: no definite diagnosis of IBD (n = 11), diagnosis of adenocarcinoma in the biopsy sample which could not be reproduced in the colectomy specimen (n = 2), a focus of micro-carcinoid instead of adenocarcinoma (n = 2), unknown date of diagnosis of IBD diagnosis (n = 1) and occurrence of CRC before IBD was diagnosed (n = 1).

Men were more frequently affected than women (male:female ratio of 3:2). Ulcerative colitis, (ileo)colonic Crohn's disease or indeterminate colitis were the underlying types of IBD in 60%, 39% and 1% of patients, respectively (table 1). The median age at diagnosis of IBD-associated CRC was 49 years (range, 21–85 years) and did not differ between ulcerative colitis and Crohn's disease patients. Concomitant PSC was found in 19 (13%) patients. In the majority of these patients (n = 15) PSC

Table 1 Patients' characteristics

	IBD-associated CRC (n = 149)	Ulcerative colitis (n = 89)	Crohn's disease (n = 59)	Indeterminate colitis (n = 1)
Sex				
Male	89 (60%)	58 (65%)	29 (49%)	1 (100%)
Female	60 (40%)	31 (35%)	30 (51%)	0 (0%)
Median age at diagnosis of IBD	29 (6–83)	30 (10–71)	29 (6–83)	70
Median age at onset of symptoms	28 (6–83)	28 (10–71)	29 (6–83)	67
Median age at diagnosis of CRC	49 (21–85)	49 (21–83)	50 (27–85)	77
Disease extent				
Unknown (ulcerative colitis)		9 (10%)		0 (0%)
Left-sided disease (ulcerative colitis)		14 (16%)		1 (100%)
Extensive disease (ulcerative colitis)		66 (74%)		0 (0%)
Unknown (Crohn's disease)			10 (17%)	
<50% segmental colitis (Crohn's disease)			17 (28%)	
>50% segmental colitis (Crohn's disease)			14 (23%)	
Pancolitis (Crohn's disease)			18 (30%)	
Primary sclerosing cholagitis	19 (13%)	16 (18%)	3 (5%)	0 (0%)

CRC, colorectal carcinoma; IBD, inflammatory bowel disease.

occurred after IBD was diagnosed. Extensive disease (inflammation extending proximal of the splenic flexure) was found in 74% of patients with ulcerative colitis. In more than half (53%) of the patients with Crohn's disease more than 50% of the colonic mucosa was involved at one moment during follow-up.

Colorectal cancers

Multiple synchronous primary colorectal cancers were found in 9% of patients (n = 14). In total, 166 carcinomas were identified in 149 patients; 11 patients had two carcinomas and in three patients three tumours were found. The initial cause of diagnosis of CRC was surveillance colonoscopy in 25 (17%) cases of which two were index colonoscopies, thus only 23 patients were part of a surveillance programme prior to diagnosis of CRC. All other diagnoses of CRC were made incidentally due to various causes (table 2).

Most cancers (51%) were located in the left colon (fig 1), mainly rectum (27%) and sigmoid colon (24%). There was no difference between ulcerative colitis and Crohn's disease concerning left or right-sided tumour location (p = 0.89). Almost all tumours, 160 out of 166, were found in colonic mucosa that was or had been inflamed. More than half of the patients (53%) had T3 tumours and 31 (18.6%) patients already had metastases when CRC was diagnosed (table 3).

Intervals between IBD and CRC

The intervals between diagnosing IBD and CRC varied from 0 to 45 years (fig 2). We observed that 33 of 149 (22%) patients developed CRC before the first surveillance colonoscopy is recommended to take place when the surveillance guideline starting points of 8 or 15 years duration of disease are followed (table 4). Ulcerative colitis, Crohn's disease and indeterminate colitis was the underlying type of IBD in 19, 13 and one patients, respectively. If the starting points of 10 or 20 years had been used, 41 of 149 patients (28%) would have developed CRC before the start of surveillance (ulcerative colitis, Crohn's disease and indeterminate colitis in 25, 15 and one patients, respectively). If the *onset of symptoms* instead of the moment of diagnosing IBD is used as starting point of disease duration, as advocated by the BSG, 25 out of 149 (17%) patients would have developed CRC before 8 or 15 years of disease. Thirty-three of 149 patients (22%) would have developed CRC if the later starting points of surveillance (10 and 20 years) had been used. In 11 patients IBD and CRC were diagnosed simultaneously. Seven of these patients had Crohn's disease and four had ulcerative colitis. If these 11 patients are excluded from analysis, then 15% of patients developed CRC before 8 or 15 years of disease duration, and 20% of patients before 10 or 20 years of disease duration. These percentages are 9% and 15%, respectively, with onset of symptoms as entry point.

Table 2 Initial cause of diagnosis of colorectal cancer (CRC)

Cause	n (%)
Surveillance colonoscopy	25 (17)
Non-surveillance colonoscopy	35 (23)
Increase of symptoms*	61 (41)
Incidental finding in colectomy specimen	20 (13)
Refractory disease	10 (7)
Proctectomy in IPAA procedure	1 (1)
Toxic megacolon	1 (1)
Stenosis	1 (1)
Perforation after colonoscopy	1 (1)
Dysplasia	6 (4)
Suspected appendicitis†	1 (1)
Suspected acute cholecystitis†	1 (1)
Abnormal laboratory findings	4 (3)
Unknown‡	2 (1)

*Symptoms include increase of abdominal pain, altered bowel habits with or without rectal blood loss.
†CRC detected during laparotomy.
‡Referrals for proctocolectomy of which the initial cause of CRC diagnosis was irretrievable.
IPAA, ileal pouch anal anastomosis.

DISCUSSION

This study demonstrates that a substantial part of all IBD-associated colorectal cancers occur before colonic surveillance should start according to BSG and AGA guidelines. Strict adherence to these guidelines will therefore lead to late detection of these "early" cancers which may reduce the efficacy of colonic surveillance in IBD.

How were starting points of surveillance determined in the AGA and BSG guidelines? In the AGA surveillance guidelines[5] no specific reference to publications is given which support abstaining from surveillance during the first decade of IBD, thus we must assume this was based on expert opinion. The BSG guidelines[6] are to a large extent a derivative of the results of a meta-analysis performed by Eaden *et al*. Based on data of 19 studies,[8–26] IBD-associated CRC risks of 2%, 8% and 18% for the respective disease durations of 10, 20 and 30 years were found. Furthermore, Eaden and Mayberry state in the BSG surveillance guideline that CRC is rarely encountered when disease duration is less than 8–10 years. This statement is based on data dating back as far as the 1960s.[23 24 27–29] Although relatively large numbers of carcinomas and person-years were included in the British meta-analysis, this study still has limitations. Two studies[9 10] in the meta-analysis included patients who had undergone subtotal colectomy for non-malignant indications, thereby eliminating the risk of cancer in the colon except the rectum. Moreover, three of 19 studies[12 17 22] excluded explicitly those patients who developed CRC within 5, 7 or 10 years of IBD duration. Despite these drawbacks, which artificially

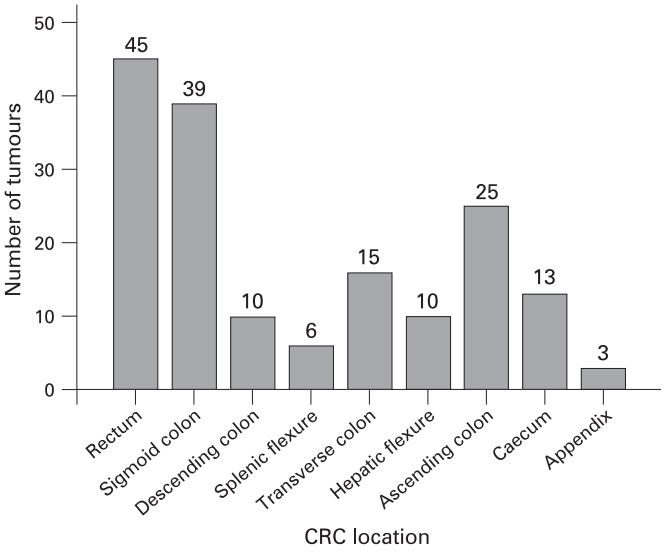

Figure 1 Location of colorectal cancer (CRC). Tumour location in the colon of all 166 carcinomas in 149 patients. Bars represent number of tumours in corresponding region of the colon on the x-axis.

reduce the risk of CRC in the first 10 years after the onset of IBD, 73 of 394 colorectal cancers (19%) found in 16 of the 19 aforementioned studies[8 11–13 15–17 20–26] occurred within an IBD duration of less than 10 years. This percentage fits remarkably well in our range of 17–28%. However, this aspect of the meta-analysis is not taken into account in the BSG surveillance guidelines. The authors might have considered CRC in recent-onset IBD not related to the chronic inflammatory condition. Another possibility is that the cumulative risk of 2% in the first 10 years of disease was regarded as too low for initiating colonic surveillance when seen from a cost-effectiveness point of view. Still, both our data and those of the meta-analysis show that approximately 20% of IBD-associated colorectal carcinomas occur in the first decade of IBD.

The AJCC tumour stage distribution (fifth edition) in our study population (table 2) did not differ from those in a population-based cohort of more than 119 000 patients with all types of colon cancer[30] and a population-based cohort of more than 1300 sporadic colon carcinomas.[31] Hence, our data do not support the general notion of a more advanced stage of cancer at diagnosis in IBD patients.

Information about medication history was collected for this group of patients. This is especially interesting with regard to the possible antineoplastic effect of 5-ASA treatment.[32] However, the retrospective design of our data collection warrants us to be prudent with its interpretation. Not all physicians meticulously registered the exact duration of medication usage. Despite this drawback and the lack of a proper control group, it is interesting to note that 119 out of 139 (10 cases unknown) patients (86%) have used a 5-ASA preparation during the course of their disease. Of these 119 patients, 64 (54%) used 5-ASA medication for more than three-quarters of their disease duration. Nevertheless, all these patients developed CRC.

Table 3 Tumour stage

Stage	n (%)
T stage	
Tis	13 (7.8)
T1	19 (11.4)
T2	21 (12.7)
T3	89 (53.6)
T4	11 (6.6)
Tx	13 (7.8)
Total	166 (100.0)
N stage	
N0	102 (61.4)
N1	26 (15.7)
N2	29 (17.5)
Nx	9 (5.4)
Total	166 (100.0)
M Stage	
M0	103 (62.0)
M1	31 (18.7)
Mx	32 (19.3)
Total	166 (100.0)
AJCC stage	
0	13 (7.8)
I	34 (20.5)
II	50 (30.1)
III	33 (19.9)
IV	31 (18.7)
Unknown	5 (3.0)
Total	166 (100.0)

Five tumours were not classifiable under AJCC stage: two were TxN0M0, two were TxNxMx, and one was TxNxM0.
AJCC, American Joint Committee on Cancer.

According to AGA and BSG guidelines IBD patients with concomitant PSC should have annual surveillance colonoscopy starting the day PSC is diagnosed. In our study population PSC was diagnosed in 19 cases (13%). These patients would have undergone immediate surveillance after diagnosing PSC so their first colonoscopy may have been performed earlier than 8/15 or 10/20 years. Correction of our data for PSC leads to small decreases in the percentages of patients with early CRC that would be missed if surveillance guidelines are followed. Instead of 22% of all patients, 20% would be missed when 8 and 15 year starting points had been applied.

The main clinical difference between sporadic and IBD-associated colorectal cancer is that the last occurs in patients with concurrent IBD. Other distinguishing clinical features are CRC development in individuals at a younger age and a higher rate of synchronous primary colorectal carcinomas.[3] A potential argument against our findings may be that the colorectal cancers, diagnosed within 10 years of onset of IBD, were in fact sporadic colorectal carcinomas. This seems very unlikely, however, because the median age of patients when CRC was diagnosed did not differ between the "early" and "late" carcinoma groups (47 years (21–83) vs 49 years (28–85)) and almost all (38 of 41) "early" tumours were found in mucosa that was or had been inflamed endoscopically and/or histologically. Of three tumours data were lacking to fully ascertain inflammation of the surrounding mucosa. This was also the case in three of the "late" tumours.

In 11 of 149 patients (6.7%) IBD and CRC were diagnosed simultaneously. We decided to include these patients in the analysis for three reasons. Firstly, we believe that it is imprudent to exclude the possibility of developing CRC within 10 years of disease duration. Too much is still unknown about inflammation-induced carcinogenesis to firmly assume that colorectal cancer does not develop within this time period. Secondly, the existence of asymptomatic colitis may have put a patient at risk without the patient or physician ever knowing. This could lead to an underestimation of disease duration. Finally, although we acknowledge that immediate surveillance would not have advanced the diagnosis of CRC in patients with synchronous diagnoses of CRC and IBD, it does support our notion that surveillance duration cannot be reliably based on disease duration.

Onset of IBD-associated symptoms, instead of the actual diagnosis, may provide a better estimation of years at risk and therefore is advised by the BSG to use as a starting point. Unfortunately, the date of onset of symptoms cannot always be retrieved and may give rise to recall bias. In the present study, the date of onset of IBD-associated symptoms was equal to the actual date of diagnosing IBD in little over a half of our patients (52%). Furthermore, date of onset of IBD-associated symptoms and the date of the actual diagnosis differed by less than 1 year in 74% of our patients. So, in only a quarter of our patients this had had some impact on timing of surveillance.

We must stress that our study was not designed to obtain data on the prevalence and risk of CRC in the entire IBD population. The required population-based cohort to answer this question is almost impossible to obtain in The Netherlands due to a lack of defined healthcare districts and a large number of patients who remain under primary care at their general practitioner. This is especially the case for mild cases of IBD. A proportion of these patients never undergoes endoscopy with

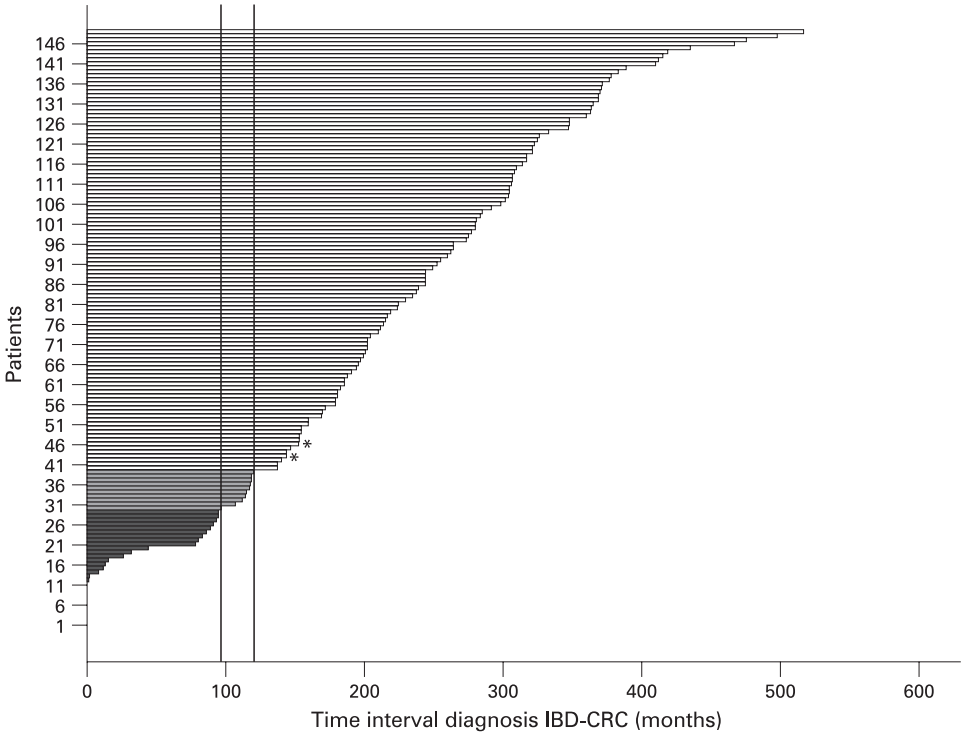

Figure 2 Time Intervals between diagnosis of inflammatory bowel disease (IBD) and colorectal cancer (CRC). Bars represent time intervals between diagnosis of IBD and CRC in months for all individual 149 patients. The left vertical line indicates the starting point of surveillance at 8 years disease duration. The right vertical line indicates the starting point of surveillance at 10 years disease duration. Black bars represent the patients with "early" CRC before 8 years disease duration. Grey bars represent additional "early" CRCs before 10 years disease duration. An asterisk indicates a patient with left-sided colitis who developed CRC before 15 or 20 years disease duration.

biopsies to confirm the diagnosis. Because our search was restricted to patients with confirmed diagnoses of IBD and CRC treated at university medical centres, our study group is not population-based. All our patients were primarily treated in, or were referred to, tertiary referral centres and therefore it is possible that our group of patients represents a subset of IBD patients with more severe disease than the general IBD population. Nevertheless, the present study provides important information on this particular subset of patients and identified all IBD patients who developed cancer over the past 15 years in this setting.

As we were well aware of the limitations of a retrospective study design, the design of this study was carefully chosen to fit our main aim. We were primarily interested in the time span between the diagnosis of IBD and the diagnosis of CRC, and evaluated how often cancer occurred in the first decade of disease. This was found to be the case in approximately one-fifth of the patients in this study.

Current AGA and BSG guidelines are solely based on duration and extent of colitis, and the presence of PSC. The structure of surveillance guidelines after a fixed period of time seems to be somewhat rigid. The results of this study show that the diagnosis of cancer is sometimes delayed when fixed starting points of surveillance are used. Not all IBD patients develop cancer though, and therefore annual or biannual colonoscopy might be over-reaching for some. We advocate a structure that stratifies patients according to the risk of developing CRC. Of interest are other risk factors for IBD-associated CRC, such as severity of disease,[33] early age of onset of IBD,[15 20] family history of CRC[34–36] and pseudopolyps[37 38] which have not (yet) been incorporated in surveillance guidelines, but could help in predicting patients who have a higher risk than others. Very intriguing in this respect is a publication by Rutter *et al*[38] which concludes that macroscopically normal-looking mucosa on colonoscopy reduces the cancer risk to that of the general

Table 4 Analysis of inflammatory bowel disease–colorectal cancer intervals in different subgroups

	8–15 years	10–20 years	8–15 years	10–20 years
	IBD–CRC interval (%)	IBD–CRC interval (%)	OoS–CRC interval (%)	OoS–CRC interval (%)
All cases				
CRC before SPoS	33 (22)	41 (28)	25 (17)	33 (22)
CRC after SPoS	116 (78)	108 (72)	124 (83)	116 (78)
Total	149 (100)	149 (100)	149 (100)	149 (100)
Ulcerative colitis				
CRC before SPoS	19 (21)	25 (28)	14 (16)	19 (21)
CRC after SPoS	70 (79)	64 (72)	75 (84)	70 (79)
Total	89 (100)	89 (100)	89 (100)	89 (100)
Crohn's disease				
CRC before SPoS	13 (22)	15 (25)	10 (17)	13 (22)
CRC after SPoS	46 (78)	44 (75)	49 (83)	46 (78)
Total	59 (100)	59 (100)	59 (100)	59 (100)

All numbers for 8–15 IBD–CRC interval and 10–20 OoS–CRC interval are the same which is purely coincidental.
CRC, colorectal cancer; IBD, inflammatory bowel disease; OoS, onset of symptoms; SPoS, starting point of surveillance.

population. In this case surveillance could be reduced for this subset of patients. At present no predictive test exists for IBD-associated neoplasia with high positive and negative predicting values just using clinical and endoscopic features of IBD patients. Integration of these features with biomarkers of colorectal neoplasia may prove to be a fruitful approach for the future. A large prospective trial is needed in which all of these features are evaluated so that surveillance guidelines can be adjusted accordingly.

In summary, we identified 149 patients with IBD-associated CRCs. Implementation of the current BSG and AGA entry points for surveillance in our patient population may lead to delay in diagnosing colorectal cancer in approximately 20% of patients. Surveillance guidelines largely based upon disease duration therefore seem to be insufficient and need to be expanded.

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