Patients with endoscopically visible polypoid adenomatous lesions within the extent of ulcerative colitis have an increased risk of colorectal cancer despite endoscopic resection.

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Abstract

Objectives: Ulcerative colitis (UC) is associated with an increased risk of colorectal cancer (CRC). Few studies have looked at long term outcomes of endoscopically visible adenomatous lesions removed by endoscopic resection in these patients. We aimed to assess the risk of developing CRC in UC patients with adenomatous lesions that develop within the segment of colitis compared to the remainder of an ulcerative colitis cohort.

Methods: We identified patients with a confirmed histological diagnosis of UC from 1991-2004 and noted outcomes till June 2011. The Kaplan–Meier method was used to estimate cumulative probability of subsequent CRC. Factors associated with risk of CRC were assessed in a Cox proportional hazards model.

Results: 29 of 301 patients with UC had adenomatous lesions noted within the segment of colitis. The crude incidence rate of developing colon cancer in patients with UC was 2.45 (95% CI 1.06-4.83) per 1000 PYD and in those with UC and polypoid adenomas within the extent of inflammation was 11.07 (95% CI 3.59-25.83) per 1000 PYD. Adjusted Hazards ratio of developing CRC on follow up in UC patients with polypoid dysplastic adenomatous lesions within the extent of inflammation was 4.0 (95% CI 1.3-12.4).

Conclusions: The risk of developing CRC is significantly higher in UC patients with polypoid adenomatous lesions, within the extent of inflammation, despite endoscopic resection. Patients and physicians should take the increased risk into consideration during follow up of these patients.

Keywords: adenomas, cancer, dysplasia, risk, ulcerative colitis

Introduction

Patients with long standing, extensive ulcerative colitis (UC) have an increased risk for developing colorectal carcinoma[1]. Since the first description by Blackstone et. al. the finding of a raised dysplastic lesion was considered an ominous finding[2]. Of 112 patients with UC in this study, 12 raised lesions with dysplasia were found and 7 (58%) of them had invasive cancer in the colectomy specimen. The term dysplasia associated lesion/mass (DALM) was coined to describe these lesions. Subsequently Bernstein et. al. in a systematic review of 10 prospective studies found that 17(43%) of 40 cases with DALM's had associated colon cancer[3].

The treatment of patients with UC and DALM's has remained controversial. Blackstone et.al. suggested that dysplasia associated with a DALM, especially a polypoid mass was an indication for colectomy in view of the increased likelihood of cancer[2]. Several subsequent studies seem to support this argument [4]. The criticism leveled at these studies was that the lesions detected were fairly advanced, and despite endoscopic biopsies not revealing a cancer, subsequent surgery and histological examination of the specimens revealed the underlying cancer. More recently a distinction has been made between sporadic adenomas which have been described as discrete well defined, sessile or pedunculated polyps resembling adenomas in patients without inflammatory bowel disease and other (non-adenoma like) DALM's which are broad based sessile, irregular, ulcerating or stricturing lesions[5]. Other studies have classed only those polyps outside the extent of histological inflammation as sporadic adenomas further adding to the confusion in terminology of these lesions [6]. The recent SCENIC guidelines suggests using the standard Paris classification for colorectal lesions along

with additional descriptors of whether the lesions was within the colitic segment , circumscribed endoscopic resectability and associated ulceration[7]. A systematic review which included 10 studies, with 376 IBD patients with resected polypoid dysplasia followed up for a mean of 54 months, reported an pooled incidence for dysplasia and CRC of 65 and 5.3 cases per 1000 patient years respectively[8].

On the basis of these studies it has been suggested that patients with endoscopically resectable raised dysplastic lesions associated with UC should not have colectomy. The recommendation of the SCENIC panel based on 9 studies reviewed (all retrospective and single arm) on the endoscopic management of polypoid dysplastic lesions during the video-endoscope era was: endoscopic resection with continued surveillance [7]. One of the major criticisms of these studies was that they were mainly single arm (no comparator) and did not take into account other risk factors for cancer. Risk of cancer in patients with UC is a dependent on disease duration[1] and also on age[9], sex[10] and extent of disease[1,9]. Risks of cancer in patients with UC are therefore best expressed on the basis of duration of disease and adjusted for risk factors. A Dutch pathology database (PALGA) study showed that the adjusted risk of developing advanced neoplasia on follow up for patients with IBD and adenomas compared to IBD patients without adenomas was 2.8 fold higher (95% CI 1.0-8.2) underscoring the need for intensive surveillance following endoscopic resection [11].

Aims of the study

The aim of this study was to compare the risk of subsequently developing colorectal cancer in patients with UC and endoscopically resectable polypoid dysplastic lesions

within the extent of histological inflammation compared to the remainder of the UC cohort.

Methods

Subjects

All adult patients with a histological diagnosis of ulcerative colitis made between 1991-2004, were identified from the histopathology database at St George's Hospital, London a larger University teaching hospital. Patients were included in the study only if they had undergone colonoscopy with segmental biopsies in this institution. Standard protocol was performed taking biopsies from all segments of the colon. Patients who were not under follow up primarily at St George's Hospital and referred with a diagnosis of colon cancer were excluded from the study. All data on endoscopy and histology was obtained from the electronic patients records of St George's Hospital. If data was incomplete or unclear in the electronic records, patient charts were traced through medical records and scrutinized. For this study, duration of follow up was defined as the time from which the histological diagnosis of UC was first confirmed to the time when the last colonoscopy with segmental biopsies was performed in this hospital, or to the time when total or subtotal colectomy was done. Follow up data noted on the electronic patient records till June 2011 was recorded (at least 7 years after the last inclusion colonoscopy). Histopathology and endoscopy reports were reviewed to detect whether patients developed further adenamtous lesions with low grade dysplasia, high grade dysplasia, or CRC during follow-up.

Since this was a retrospective study we did not attempt to distinguish between ALM's and DALM's. Patients with raised endoscopically resectable dysplastic polypoid lesions seen within the extent of colonic inflammation with no evidence of flat dysplasia adjacent or remote to the polypoid lesion were included in the UC with adenomatous polyp arm. All other patients with UC were placed in the comparison cohort. The endoscopy report was used to determine the location and size of the polyp and whether the polyp was resected endoscopically. Standard snare resection techniques were used for stalked polyps and endoscopic mucosal resection after submucosal injection of saline or a hypertonic solution was used for sessile and non-polypoid lesions based on the endoscopists choice. Completeness of resection was based on endoscopist's impression where available.

Dysplasia was classified as either low-grade or highgrade, according to standard criteria and definitions based on Ridell et,al[12]. Histopathology reports were based on routine reporting by a GI histopathologists and a discussion of the pathology at the weekly multi-discliplinary team meeting where the pathology would be reviewed bya second GI hiatopatholgist.

Statistical analysis

Statistical analysis was done using SPSS version 21 (IBM corporation, USA) statistical package. All baseline values were recorded as mean ± standard deviation (SD) or percentages. Crude incidence rates (number of cases during the period of observation divided by the total person-time of observation) for each group were calculated and expressed as number of cases per 1000 persons years of disease duration (PYD).

The Kaplan–Meier method was used to estimate cumulative probability (1 minus survival free) of subsequent CRC. Comparisons between groups were made using Breslow log-rank tests. The cox proportional hazards regression model was used to assess the associations of clinical variables on development of CRC. The following variables were assessed in these models: 1) presence of a endosocpically resectable polyp versus none detected; 2) disease extent (extensive versus other); 3) age at diagnosis and 4) gender (male or female). Results are reported as hazard ratios (HR) with 95% confidence intervals (95% CI).

Results

Of the 751 patients with a histological diagnosis of UC made between 1991-2004, 397 patients had at least one colonoscopy with serial mucosal biopsies during this period. The remainder did not fulfill the inclusion criteria either because they had only a rigid or flexible sigmoidoscopy or had an incomplete colonoscopy either because they did not tolerate the procedure or had poor bowel preparation. A further 96 did not have any further follow up at St George's hospital till June 2011 and were excluded. Of the 301 patients included 29 had endoscopically detected polypoid dysplastic lesions within the extent of colonic inflammation at some point. A further 5 patients had adenomas outside the extent of UC and were included in the comparison cohort of all other UC patients. Table 1 outlines the patient characteristics of these two groups and Figure 1 provides a flow chart showing the outcomes at end of follow up. Of the 29 patients with polypoid adenomatous lesions within the extent of colitis, 27 had their lesions endoscopically resected. Table 2 outlines the salient characteristics of the polyps detected in this group. One patient had a sessile broad based polyp in the rectum with low grade

dysplasia on endoscopic biopsies and refused any endoscopic or surgical procedures and on follow up colonoscopy 27 months later had no progression of the lesion on repeat endoscopic biopsies. Another patient with a sessile polypoid lesion in the descending colon with low grade dysplasia on endoscopic biopsies opted to have a colectomy, the specimen revealed no evidence of any invasive cancer or high grade dysplasia. Five patients developed invasive adenocarcinoma in the same segment between 14-48 months after the initial endoscopic resection. Ten patients had recurrent polypoid dysplastic lesions noted in a median follow up of 49 months (range 12-108 months) after the initial endoscopic resection, which were also endoscopically treated. Five of these 29 patients had high grade dysplasia on their initial endoscopic resection specimen of which 2 subsequently developed carcinoma on follow up.

The comparison cohort consisted of 272 patients with UC with no polypoid dysplastic lesions within the extent of the colitis. There were 5 adenocarcinomas detected of which 1 had prior high grade dysplasia detected only by random colonoscopic biopsies. Eight patients had low grade dysplastic lesions (not visible endoscopically) detected only on random colonoscopic biopsies, none of which had progressed till the end of follow up.

The crude incidence rate of developing colon cancer in patients with UC was 2.45 (95% CI 1.06-4.83) per 1000 PYD and in those with UC and polypoid adenomas within the extent of inflammation was 11.07 (95% CI 3.59-25.83) per 1000 PYD.

Figure 2 shows the Kaplan Meir curve of the cumulative risk of developing CRC comparing patients with a polypoid dysplastic lesion within the extent of inflammation to those without (log rank test p=0.007). Table 3 shows the Cox proportional hazards

analysis of the factors associated with the development of CRC. Presence of a polypoid dysplastic lesion within the extent of colitis was associated with 4 fold risk in the risk if subsequent CRC and this risk was maintained even after multivariate analysis adjusting for extent, age of diagnosis and gender.

Discussion

Patients with ulcerative colitis with an endoscopically resectable dysplastic polypoid lesions within the extent of colonic inflammation, , have nearly a 4 fold risk of subsequently developing cancer compared to a cohort of UC patients not having similar polypoid dysplastic lesions. While 5 patients (17%) subsequently developed a carcinoma, of the remaining 24 patients, 10 (42%) had a recurrent polypoid dysplastic lesions detected on follow up which is similar to the findings of Odze et al[13]. We believe that taking the total duration of disease and not just the follow up period post polypectomy or excision of lesion should be taken into account when determining risk. We also adjusted the risk estimate for age, sex and extent of disease. This reflects a more accurate perception of the risk of colorectal cancer in these patients. Our results are therefore similar to that by the Mayo group who found that the 5-year cumulative risk of subsequent colonic neoplasia after endoscopic resection in both those with sporadic adenomas as well as those with adenoma like masses to be 68.5% and 70.6% respectively[6]. A Dutch pathology database study showed that the adjusted risk of developing advanced neoplasia on follow up for patients with IBD and adenomas compared to IBD patients without adenomas was 2.8 fold higher (95% CI 1.0-8.2) which is also reflected in the results of the present study [11]. A systematic review which included 10 studies, with 376 IBD patients with resected polypoid dysplasia followed up

for a mean of 54 months, reported an pooled incidence for dysplasia and CRC of 65 and 5.3 cases per 1000 patient years respectively[8].

As with all retrospective analyses there are several limitations to our study. We have not been able to match for confounding factors like family history of colon cancer[14] and medication usage which could affect the risk[15]. A study from the Mayo clinic however did not find any association between 5ASA use and subsequent development of colorectal neoplasia after endoscopic resection [6]. The endoscopic procedures were performed by different endoscopists, which is a potential factor in influencing the completeness of resection and subsequent risk of recurrence although all were appropriately accredited. Additionally it was no always possible to determine completeness of excision based on retrospective evaluation of endoscopy reports as this was not always explicitly commented on in reports. Diathermy artefacts could also preclude the histopathologists from commenting on completeness of excision especially when small polyps were resected with a hot biopsy forceps (as was the practice at the time of the study) or when larger polyps were resected piecemeal. However all procedures were performed by accredited endoscopists and reflects real world practice in a standard National Health Service setting.

Another source of bias could have arisen because we interpreted the histology on the basis of the prior routine histology report and discussion of the histology at a multi-disciplinary meeting. Due to limited storage capacity, slides over 10 years old are discarded by our histopathology department precluding retrospective re-examination. Since all the original sections could not be reviewed, the prior routine reports were used throughout. We believe that this is an entirely reasonable approach as the clinical

treatment of these patients was based on the original reports and reflects routine clinical practice. Various methods have been described using endoscopic and histopathological techniques including immunohistochemistry to characterize these lesions as sporadic adenomas and adenoma like masses with no current consensus on the reliability of these various criteria. We have avoided re-categorizing these lesions retrospectively, mainly because we feel that from a clinical perspective these lesions form part of the same spectrum, analogous to that seen in sporadic adenomas. Lesions which are non-resectable are likely to be bigger and harbor cancer, while endoscopically resectable lesions are likely to be smaller and benign[16]. None of our patients had cancer noted in the initial endoscopic resection specimen. Additionally a study from the Mayo clinic showed that the risk of subsequent neoplasia after endoscopic reaction was similar in UC patients classed as having sporadic adenomas as well as those with adenoma like masses[6].

The median number of biopsy specimens in this study was 8, which is very similar to practice elsewhere in the UK. Self-reported number of biopsies in a survey of UK gastroenterologist revealed that 57% take fewer than 10 biopsies per patient[17]. The St Mark's group also reported a median number of 8 biopsies in their surveillance programme[16]. Our figures are therefore representative of UK clinical practice and can be generalizable to most clinical practices. This could have led to lower identification of dysplasia but conversely many studies have shown an extremely low yield of dysplasia from non-targeted biopsies compared to targeted biopsies suggesting that the incremental benefit from multiple non targeted biopsies is small[7,18]. As this study was a single center retrospective study which depended on patient follow up in a single

institution and while all patients underwent colonoscopy with biopsies, this was not done in a protocolized fashion as evidenced by the low median number of random biopsies taken. These factors however are likely to bias the study towards under detection of the outcomes of interest.

Polypectomy has been suggested to be adequate therapy for UC patients with adenomatous polyps which endoscopically or histologically resemble sporadic adenomas. This study demonstrates that there is an increased risk of developing colorectal cancer in this patient group with dysplastic polyps within the extent of inflammation compared to the rest of the general UC population. Patients and physicians need to be aware of this increased risk before deciding on treatment options. Complete endoscopic removal and subsequent strict endoscopic surveillance protocols are therefore needed after endoscopic resection of adenomatous lesions in patients with ulcerative colitis. Since this is a single center retrospective study with small numbers, further prospective multi-centre studies are required, taking into account risk factors like family history of colorectal neoplasia, presence of primary sclerosing cholangitis, use of thiopurine and 5-aminosalicylate drugs and duration and extent of UC to validate these observations.

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Table 1: Patient characteristics of the 301 ulcerative colitis patients with and without a polypoid dysplastic lesion within the extent of inflammation.

	UC with dysplastic adenomatous polyp within extent of inflammation	UC controls without adenomatous polyps within extent of inflammation
Number	29	272
Age at diagnosis in years (±SD)	49 (17)	38(20)
Duration of colitis in years (±SD)	16(10)	12(11)
Male (%)	18(62)	144(53)
No. with Extensive colitis (%)	17(59)	144(53)
Number of random biopsies: median	12	8

Table 2: Characteristics of the polyps within the extent of inflammation detected in patients with ulcerative colitis.

Number of patients with polyps	29
Number with > 1 polyp (%)	10 (34)
Polyp location: number(%)	
Caecum	3 (10)
Right Colon	3 (10)
Transverse	3 (10)
Left Colon	20 (70)
Polyp architecture: number(%)	
tubular	23 (79)
tubulovillous	05 (17)
villous	1 (4)
Size in mm : median(range)	10 (5-35)
Grade of dysplasia: number (%)	
Low grade dysplasia	22 (76)
Focal high grade dysplasia	2 (7)
High grade dysplasia	5 (17)

Table 3: Cox Proportional Hazard Analysis of the Association Between the Presence of a polypoid dysplastic lesions and the development of subsequent colorectal cancer.

Factor	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Dysplastic polyp within extent of inflammation	4.1 (1.3-12.7)	4.0 (1.3-12.4)
Age (>40 year vs <40 years)	2.3 (0.3-17.7)	1.6 (0.2-13.3)
Gender (male vsfemale)	1.4 (0.5-4.4)	1.3 (0.40-3.3)
Disease extent (extensive vs rest)	3.2 (0.7-14.7)	3.2 (0.7-14.6)

Figure Legend:

Figure 1: Flow chart showing the final outcomes of patients included in this study at the end of follow up.

Figure Legend:

Figure 2: Kaplan-Meier curve comparing the development of CRC between UC patients with polypoid dysplastic lesions within the extent of inflammation and the reference UC population.

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Disease extent (extensive vs rest)	3.2 (0.7-14.7)	3.2 (0.7-14.6)

Figure

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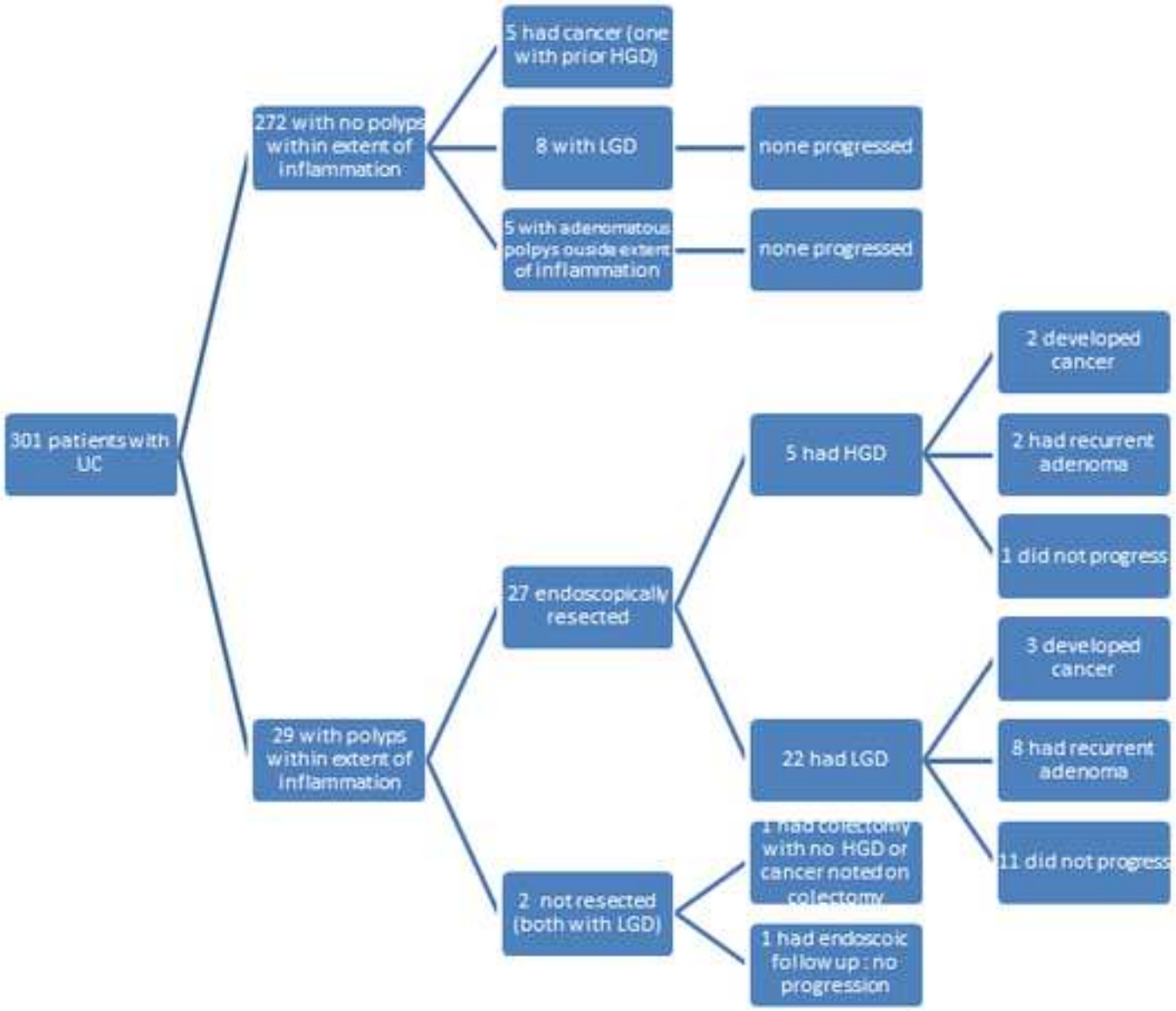

Figure

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