Temporal trends in colon neoplasms in patients with primary sclerosing cholangitis and ulcerative colitis

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Abstract

Background and aim: Surveillance for colon cancer is recommended in patients with primary sclerosing cholangitis (PSC) and ulcerative colitis (UC). It is unclear whether characteristics of colon neoplasia have changed over time. The aim of the study was to examine the temporal trends in colon neoplasia in patients with PSC and UC.

Methods: A total of 167 patients followed up at our institution between 1985 and 2011, 55 of these with neoplasia detected on colonoscopic biopsy were identified. Characteristics of patients with colon neoplasia in PSC–UC were studied for two different time periods: 1985–1998 (early cohort) compared to 1999–2011 (recent cohort).

Results: The median age at diagnosis of colon neoplasms was 53 years (median IQR, 43–63). The baseline characteristics were similar in both cohorts. The colonic neoplasms that developed in PSC–UC patients were spread throughout the colon on colonoscopy, while there was predominant right sided distribution on colectomy in both cohorts. (81.7% vs. 18.3%, p<0.001) Compared to the recent cohort, both the PSC (17 vs. 11 years, p=0.02) and UC duration (20 vs. 12 years, p=0.02) were longer in the early cohort. There were no differences in the grades and stages of cancer diagnosis. In addition, no differences in transplant-free survival or UC characteristics were revealed.

Conclusions: With annual colonoscopic surveillance, dysplasia and cancer in patients with a combined diagnosis of PSC/UC is being diagnosed in patients with a shorter duration of these conditions. The nature and the location of neoplasia have, however, not changed.

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Abbreviations: 5-ASA, 5-aminosalicylic acid; CD, Crohn’s disease; CI, confidence interval; ERCP, endoscopic retrograde pancreatobiliary cholangiography; IBD, inflammatory bowel disease; IC, indeterminate colitis; MRCP, magnetic resonance pancreatobiliary cholangiography; OR, Odds ratio; OLT, orthotopic liver transplantation; PSC, primary sclerosing cholangitis; UC, ulcerative colitis

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1. Introduction

Primary sclerosing cholangitis (PSC) is a chronic, cholestatic hepatobiliary disease commonly seen associated with underlying inflammatory bowel disease (IBD), most commonly ulcerative colitis (UC). Approximately 70% to 80% of patients with PSC have co-existing IBD, while 1.4% to 7.5% of patients with IBD develop PSC. Patients with UC and concomitant PSC have a distinct clinical presentation with a higher prevalence of backwash ileitis, pancolitis, colorectal neoplasia, and overall have a poorer survival than patients without concomitant PSC. Patients with PSC–UC also develop pouchitis and pre-pouch ileitis after restorative proctocolectomy compared to patients without PSC.

Patients with PSC undergo colonoscopy with biopsy at diagnosis and then every 5 years if no UC is identified, and annually if UC is identified. Patients with IBD are prone to an increased risk of colorectal neoplasia especially when they had IBD for more than 10 years, early onset of the disease and patients with extensive involvement of the colonic mucosa. Several studies have shown that in patients with IBD, concurrent PSC increases the risk of developing colitis-associated CRC. The 10-year and 20-year risk of developing colorectal neoplasia has been reported as 14% and 31%, respectively. The initial clinical presentation of PSC at the time of diagnosis seems to have changed during the recent years. The widespread use of biochemical liver tests in routine screening and the use of the non-invasive magnetic resonance cholangiopancreatography (MRCP) in the last decade may account for patients with PSC being diagnosed at an earlier and more asymptomatic stage of disease. Similarly since the introduction of guidelines for yearly colonoscopy in patients with PSC–UC, the location and relationship of colon neoplasms to PSC–UC disease duration may have changed in the recent cohort. We have previously studied the relationship between the severity of PSC and colon neoplasia in this cohort of patients. As to whether, the more aggressive surveillance that likely ensued after the establishment of these guidelines has changed the pattern and presentation of neoplasia has however not been well evaluated.

Since 1998, the practice at our institution has been to recommend annual surveillance colonoscopies for PSC patients with concomitant IBD. The aim of this study was to evaluate the location and clinical features of colon neoplasia in patients with PSC–UC during the last 25 years, and especially whether the surveillance strategy since 1998 has led to changes in the pattern of detection of colonic neoplastic changes.

2. Patients and methods

2.1. Patients

The historical cohort study was approved by the Cleveland Clinic Institutional Review Board. A prospectively maintained EDIT (Electronic Data Interface for Transplantation) database has accrued information on all patients who underwent OLT at the Cleveland Clinic. Patients with PSC and UC who required OLT were identified from the database. Patients with PSC and UC who did not require OLT were identified using the IBD database. A total of 225 patients with PSC and UC were obtained from the database. 58 patients with UC who did not have adequate follow-up at the Cleveland Clinic were excluded from the study. Finally 167 patients with PSC–UC were included in the study. Among these patients, we identified 55 patients with UC and dysplasia and/or colon cancer identified on colonoscopy for inclusion in our study analysis. We classified patients with colon neoplasia in PSC–UC into two different time periods: 1985–1998 (early cohort) and 1999–2011 (recent cohort). Since annual colonoscopies have been performed for PSC patients with a combined diagnosis of IBD since 1998 at our institution, we used this as the time line of separation for the two cohorts.

2.2. Inclusion and exclusion criteria

Inclusion criteria were as follows: 1) age older than 18 years, 2) UC, 3) presence of PSC with or without LT, and 4) presence of dysplasia and/or colon cancer on colonoscopy. Exclusion criteria were patients with CD/indeterminate colitis and patients with UC who did not have follow-up at the Cleveland Clinic or were in the transplant list and did not get a liver transplant. UC patients who underwent OLT for other liver diseases other than PSC were excluded. In patients who underwent retransplantation for PSC recurrence were also excluded.

2.3. Diagnostic criteria

PSC was defined as the presence of intra- and/or extrahepatic bile duct abnormalities in the form of beading, duct ectasia, and strictureing of the intra- or extrahepatic bile ducts documented in the medical record from endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography, and/or liver biopsy. Small duct PSC was defined when there were histological features consistent with PSC on liver biopsy in the absence of characteristic radiological features, and clinical cholestasis with persistently elevated serum alkaline phosphatase levels for greater than 6 months.

The diagnosis of UC was confirmed with characteristic endoscopic examination of inflammation as well as from compatible histological examination described before.

2.4. Demographic and clinical variables

Demographic and clinical variables were studied from patient medical records including age, gender, ethnicity, smoking and alcohol history, and family history of IBD, PSC, or liver/colon cancer in first degree relatives. The clinical variables were defined as follows — “duration of UC” defined as the time from the diagnosis of UC to the time of last clinical follow-up, “family history of IBD” — CD or UC in first degree relatives. “Smoking” — smoking more than 7 cigarettes a week, “Alcohol use” defined as more than 2 drinks a day, extent of UC “Extensive colitis” — endoscopic, macroscopic or microscopic evidence of disease proximal to the splenic flexure. The use of long-term medical therapy including corticosteroids, immunomodulators including azathioprine/6-mercaptopurine was documented. This was defined as the type of treatment used during the whole follow-up period with the use of particular medication for at least 6 months. The follow-up period was obtained from the date of
Primary sclerosing cholangitis, ulcerative colitis and colon neoplasia

3. Results

3.1. Demographic and clinical characteristics

The basic demographic and clinical information including age, sex, race, UC duration from diagnosis, PSC duration from diagnosis and colonic extent of UC is summarized in Table 1.

The 55 patients with PSC and UC with colonic neoplasia included 19 female and 36 male patients. The median age at diagnosis of PSC was 38 years (Median IQR, 30.5–46). A total of 44 (80%) patients received UDCA therapy for their liver disease. 52 (94.5%) of patients with colon neoplasms had extensive colitis in the past.

Thirty-nine patients had a history of UC, which preceded the diagnosis of PSC, while 2 patients subsequently developed UC after an initial diagnosis of PSC. UC became evident at the same time as PSC in 14 patients.

3.2. Timing of diagnosis of PSC and UC

There were 18 patients in the early cohort and 37 patients in the recent cohort. In the early cohort, UC was diagnosed before PSC in 14 patients (77.8%) compared to 25 patients (67.6%) in the recent cohort. Similarly, PSC was diagnosed before UC in the early cohort in 1 patient (5.6%) compared to 1 patient (2.7%) in the recent cohort. Both diseases were diagnosed simultaneously more often in the recent cohort as compared with the early cohort [11 (29.7%) versus 3(16.7%)].

3.3. Colonic dysplasia and carcinoma

Patients with PSC and UC were followed for a median period of 13 years (IQR, 9.5–19 years). On colonoscopy, in the early cohort, low grade dysplasia and high grade dysplasia were seen in 6 (33.3%) and 7 (37.9%) respectively, while colon cancer was seen in 5 (27.8%) patients. In the recent cohort, low grade dysplasia and high grade dysplasia were seen in 19 (51.4%) and 9 (24.3%) respectively, while colon cancer was seen in 9 (24.3%) patients. Table 2 summarizes the findings on colonoscopy.

3.4. Colonoscopy findings

Among the patients with colon neoplasia on colonoscopy, 14/55 patients had polypoid lesions at colonoscopy and colon carcinoma was diagnosed on colonoscopy in these patients. The findings on colonoscopy in both the early and recent cohorts are summarized in Table 2. 9/55 patients had adenoma like lesion/mass on colonoscopy. All the adenoma like lesions/mass occurred in the area of colitis. The remaining 32/55 patients in this study had no evidence of adenoma like neoplasia at colonoscopy. All these patients had flat dysplasia within the area of colitis on routine surveillance colonoscopies.

3.5. Location trends of colon neoplasm in PSC–UC

Both the cohorts were very similar except for the duration of PSC, UC and duration of PSC–UC all of which were significantly longer in patients in the early cohort than the late cohort. The
distribution of colon neoplasms on colonoscopy was very similar in both cohorts. (Table 2)

Five patients had flat high grade dysplasia in their colonoscopy and colectomy which was done for steroid dependent/refractory disease. The remaining patients underwent colectomy for dysplasia/cancer. Of the 36 patients with definite neoplasms found on the colectomy specimen, 38 lesions were identified as some patients had multifocal disease. If individual lesions are separately accounted for, 31 (81.6%) were classified as proximal, while 7 lesions (18.4%) were distal. The predominance of right sided lesions was observed both in the early and recent cohorts (P<0.001). Table 3 summarizes the findings on colectomy.

### 3.6. Staging of cancer

The American Joint Committee on Cancer (AJCC) staging system for colon cancer was compared for the two cohorts. In the early cohort, 1 patient had stage I cancer, while 2 patients had stage II and 5 had stage III cancer. In the early cohort, there was no significant difference in the grade of cancer. The cancer was moderate to well differentiated in 4 (80%) in the early cohort as compared to 7 (87.5%) in the recent cohort. (P=0.39).

### 3.7. Severity of PSC and colonic neoplasia

The relationship between the severity of PSC defined by the requirement for OLT and the development of colon neoplasia in both cohorts was also evaluated. There was no significant difference in the severity of PSC when comparing the early and recent cohorts. The transplant-free survival was no different when comparing the early and recent cohorts (P=0.57) (Fig. 1).

### 4. Discussion

To our knowledge, this is the first study looking at changes over time in the clinical features of a large cohort of PSC-UC...
and colon neoplasia patients. This study highlights that there are discrepancies between the colonoscopy and colectomy findings. This study demonstrated that colon neoplasms were seen throughout the colon on colonoscopy. However in the colectomy specimens, there was a predominance of right sided lesions in both the early and recent cohorts. Sampling error may be responsible for the lack of dysplasia on colectomy that was found on initial colonoscopy. Compared to the recent cohort, the duration of both PSC and UC prior to the development of neoplasia (both on colonoscopy biopsies and colectomy) was much longer in the early cohort. However the stage and the grade of cancers were no different and the survival was similar for the two cohorts.

With the advent of non-invasive modalities like MRCP, patients with abnormal liver biochemistry are increasingly screened for hepatobiliary abnormalities much more aggressively. \(^{19}\) Despite this, the age of diagnosis of PSC did not differ between the two cohorts. Our findings of the increased risk of colon neoplasia in PSC-UC are consistent with those of several studies that showed that the risk of colorectal neoplasia among PSC patients with IBD.\(^{12-18}\) Also, we found that neoplasms were equally distributed throughout the colon on colonoscopy. Although the colon neoplasms on colonoscopy were equally distributed, when the lesions were identified during colectomy, 81.6% of patients had right sided colon neoplasia consistent with prior studies in PSC–UC patients.\(^{12-17}\) The putative reason proposed is that PSC is associated with defective hepatic bile acid excretion leading to alterations in the enterohepatic circulation, causing increased exposure of primary bile acids to intestinal bacteria, and heightened conversion of primary into secondary bile acids in the proximal colon which have been shown to be carcinogenic. The right sided predominance was observed both in the early and recent cohort.

Both diseases were diagnosed simultaneously more often in the recent cohort as compared with the early cohort which may reflect the increased awareness among physicians of the association between PSC and UC. We also observed that when compared to the recent cohort, the duration of both PSC and UC before the development of neoplasia was much longer in the early cohort. Patients in the recent cohort received more surveillance colonoscopies resulting in neoplasia being detected over a shorter duration of UC and PSC is a potential explanation. This premise is supported by the finding of a trend towards more colonoscopies in the recent cohort. However, we must also remember the fact that surveillance colonoscopies only at our institution were recorded and not all follow-up colonoscopies were done at our institution. It is important to understand that the routine screening/surveillance protocol in our institution is to use white light endoscopy for dysplasia surveillance in all UC patients. In fact, none of our patients underwent advanced imaging techniques including chromo-endoscopy in our recent cohort. Thus advent of

### Table 2
Comparison of colon neoplasia diagnosed before 1998 and after 1998 on colonoscopy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early cohort (before 1998) N=18 (32.7%)</th>
<th>Recent cohort (after 1998) N=37 (67.3%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>9 (50.0%)</td>
<td>15 (40.5%)</td>
<td>0.57</td>
</tr>
<tr>
<td>Low grade dysplasia</td>
<td>3 (Flat)</td>
<td>13 (Flat)</td>
<td></td>
</tr>
<tr>
<td>High grade dysplasia</td>
<td>4 (Flat)</td>
<td>2 (Flat)</td>
<td></td>
</tr>
<tr>
<td>Colo-rectal cancer</td>
<td>2 (Flat)</td>
<td>0 (Flat)</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>9 (50.0%)</td>
<td>17 (45.9%)</td>
<td>1</td>
</tr>
<tr>
<td>Low grade dysplasia</td>
<td>3 (Flat)</td>
<td>6 (3 DALM(^{a}))</td>
<td>0.16</td>
</tr>
<tr>
<td>High grade dysplasia</td>
<td>3 (1-DALM(^{a}), tubulovillous adenoma)</td>
<td>2 (Flat)</td>
<td></td>
</tr>
<tr>
<td>Colo-rectal cancer</td>
<td>3 (Flat)</td>
<td>9 (Flat)</td>
<td></td>
</tr>
<tr>
<td>Multi-focal</td>
<td>0 (0%)</td>
<td>5 (13.5%)</td>
<td></td>
</tr>
<tr>
<td>Low grade dysplasia</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>High grade dysplasia</td>
<td>0</td>
<td>5 (DALM(^{a}))</td>
<td></td>
</tr>
<tr>
<td>Colo-rectal cancer</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) DALM—dysplasia associated lesion or mass.

### Table 3
Comparison of colon neoplasia diagnosed before 1998 and after 1998 on colectomy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early cohort (before 1998) N=12 (36.9%)</th>
<th>Recent cohort (after 1998) N=26 (63.1%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colectomy findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>4 (35.7%)</td>
<td>3 (11.5%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Low grade dysplasia</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>High grade dysplasia</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Colo-rectal cancer</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>8 (60%)</td>
<td>23 (88.5%)</td>
<td></td>
</tr>
<tr>
<td>Low grade dysplasia</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>High grade dysplasia</td>
<td>2(^{a})</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Colo-rectal cancer</td>
<td>3(^{b})</td>
<td>8(^{b})</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) Two patients had multi-focal lesions with high-grade dysplasia in their colectomy.

\(^{b}\) One patient in the recent cohort with colorectal cancer was awaiting colectomy at the time of analysis.
newer imaging techniques does not explain the shorter disease duration before diagnosis of dysplasia.

According to the American Gastroenterology Association, extensive colonic biopsies should be used to screen for dysplasia and that the screening interval should be individualized between 1 and 3 years. Chromoendoscopy was recommended as an alternative to random biopsies for endoscopists with expertise with the technique. However dye-based chromoendoscopy also has some potential limitations, as it harbors additional costs for the equipment needed for dye spraying and is a time consuming procedure. Additionally, the dye often does not coat the entire surface and it does not allow for a detailed analysis of sub epithelial capillary network, which is an important feature in the early diagnosis of gastrointestinal neoplasia. After using both while light and chromoendoscopy, we have personally observed that a good, careful white light examination and plenty of biopsies throughout the colon along with careful examination of suspicious lesions is effective in detecting dysplasia. However, we do understand the limitations of it and future studies to explore advanced imaging techniques in the detection of dysplasia are required.

Our study is clinically significant for a number of reasons. This study highlights that the distribution of colon neoplasms were seen throughout the colon on colonoscopy. However there was right sided predominance in lesions identified on colectomy. Approximately 50% of patients in the recent cohort had low grade dysplasia. Also 18 patients with lesions identified on colonoscopy did not have any dysplasia identified in their colectomy specimen. Most of these low grade dysplasia lesions were not identified in colectomy. Similar results were found in a previous study from the Mayo Clinic in which 13% of patients with dysplasia on colonoscopy did not have any in the colectomy specimen. Thus there was discrepancy between the findings on colonoscopy and colectomy findings. One reason which could be postulated is that there could be sampling error that dysplasia found on initial colonoscopy could not be found on colectomy. The colon was inflamed in only 5 patients. The remaining patients did not have significant colon inflammation at the time of surveillance colonoscopy. The diagnosis of dysplasia in our institution is routinely done by two pathologists as suggested by many IBD societies. It would be very difficult to say whether these were sampling error or false positives. It was interesting that colonoscopy found more dysplasia than during colectomy. In a recent study of 121 patients with low grade dysplasia, 7 patients progressed to colorectal cancer and 8 patients progressed to high-grade dysplasia. The authors concluded that in patients with long-standing, extensive UC, distal low grade dysplasia is more common and progresses more rapidly to advanced neoplasia than proximal low grade dysplasia. However they had excluded patients with PSC in the study. Thus the natural history of low grade dysplasia in PSC needs to be explored to understand it better. Even though we did not find dysplasia in one-third of patients, given the current evidence, it would be very difficult to recommend surveillance colonoscopies in shorter intervals rather than colectomy, particularly in the United States. However, further studies needs to be done to understand the clinical implications and significance of low-grade dysplasia in PSC and UC patients as some patients may go for colectomy unnecessarily while in some patients these patients may have their dysplasia detected early enough to prevent significant morbidity and mortality. Also development and routine implementation of newer techniques in colonoscopy to detect dysplastic lesions such as narrow band imaging and chromoendoscopy may improve diagnostic modalities to help improve surveillance colonoscopy. We also observed that the grade and the stage of cancers have remained stable over time.

There are certain limitations of our study. The study population was recruited from a subspecialty tertiary care referral center. This contributes to a selection bias. Since PSC is a disease with an insidious onset and a presumable lengthy asymptomatic phase, the date of diagnosis of PSC is to some extent driven by the awareness of individual physicians. Also UC in PSC has a long subclinical phase and the duration of colitis in the PSC population may have been similarly underestimated. We did not study the impact of surveillance colonoscopies on the risk of colon neoplasia because patients often obtained colonoscopies at outside institutions. Nevertheless, this is one of the largest studies on colon neoplasia in patients with PSC and UC that highlights the temporal trend in colon neoplasia remained stable over the last three decades.

To conclude, the findings of this study suggest that PSC–UC is associated with a right-sided predominance of neoplastic lesions. Although the clinical presentation has remained stable over time, colonic neoplasia in PSC–UC is being detected after a shorter duration of PSC and UC with the introduction of aggressive colonoscopic surveillance.

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Conflict of interest

The authors declared no financial conflict of interest.

Specific author contributions

Study concept and design, paper preparation and revisions—U Navaneethan.
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Study design, study concept and critical revisions—Bret A Lashner.

Data monitoring and paper preparation—Feza H Remzi.
Study design, study concept and critical revisions—Bo Shen.
Study design, study concept and critical revisions—Ravi P Kiran.

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