Colorectal cancer screening and surveillance in Crohn's colitis

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Abstract

Aims: To assess colonoscopic screening and surveillance for detecting neoplasia in patients with long-standing colonic Crohn's disease (CD).

Patients and Methods: Colonoscopy and biopsy records from patients with colonic CD were evaluated at the Cedars-Sinai Inflammatory Bowel Disease Center during a 17-year period (1992-2009).

Results: Overall, 904 screening and surveillance examinations were performed on 411 patients with Crohn's colitis (mean 2.2 examinations per patient). The screening and surveillance examinations detected neoplasia in 5.6% of the patient population; 2.7% had low-grade dysplasia (LGD) (n = 11), 0.7% had high-grade dysplasia (HGD) (n = 3), and 2.2% had carcinoma (anal carcinoma n = 3; rectal carcinoma n = 6). Mean age of CD diagnosis was 25.6 ± 0.8 years in those with normal examinations, compared to 17.7 ± 2.7 years (p < 0.001) in those with HGD, 36.8 ± 1.43 in those with LGD (p = 0.021) and 28.3 ± 3.24 years in those with any dysplasia/cancer (p = 0.034). Disease duration in patients with normal examinations was 19.1 ± 0.5 years, compared to 36.8 ± 4.4 years (p < 0.001) in HGD, 16.8 ± 2.59 in those with LGD (p = 0.253) and 30.68 ± 4.03 years in those with any dysplasia/cancer (p = 0.152). The mean interval between examinations was higher in HGD.
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1. Introduction

Patients with chronic inflammatory bowel disease (IBD), particularly those with long-standing and extensive ulcerative colitis (UC), are at an increased risk for the development of colonic dysplasia and carcinoma.

Colorectal cancer was first reported as a complication of “cicatrizing enteritis” (regional enteritis) in 1948 and has since been described in only a number of reports. Population-based studies and a recent meta-analysis have suggested that patients with CD have an increased risk of colorectal cancer and small bowel carcinoma. There is also data to support that the risk of colorectal cancer in Crohn’s colitis is significantly higher than in the general population, and is similar to the risk in UC of similar duration and severity. Most notably, Friedman et al. recently published a large prospective study corroborating the increased risk of colorectal cancer in CD. Other studies, however, have reported no association between CD and colorectal cancer risk. This lack of association may have been secondary to clinical factors and potential flaws in the design of these studies, including short duration of follow up, proctocolectomy in a high proportion of patients with symptomatic colitis, and inclusion of patients with isolated small bowel disease.

While the yield of screening and surveillance colonoscopy for neoplasia detection has been widely reported in patients with UC, only one study exists—to the best of our knowledge—with a follow up of the same patient cohort, which evaluated these outcomes in patients with Crohn’s colitis. In these studies, the authors reported a high incidence of dysplasia and cancer in long-standing Crohn’s colitis. In the most recent, longer follow-up of a cohort of 259 patients with extensive Crohn’s colitis, Friedman et al. reported a 7% and 14% incidence of definite dysplasia or cancer on screening and surveillance examinations, respectively. Herein, we report our experience with the yield of screening and surveillance colonoscopy in 411 patients over 17 years with colonic CD at a tertiary referral IBD center.

2. Methods

A CD patient database at the Cedars-Sinai Inflammatory Bowel Disease (IBD) Center was reviewed for colonoscopies and biopsies performed between January 1992 and July 2009 from patients with long-standing colonic Crohn’s disease. The diagnosis of CD was established using standard diagnostic criteria according to Lennard-Jones et al. Our clinical practice is to offer colonoscopic screening and surveillance for all patients with long-standing CD (8 or more years of duration) involving greater than 1/3 of the colon. Disease distal to the splenic flexure was defined as left-sided Crohn’s colitis. Patients with disease limited to the small bowel, or small bowel disease with only limited colonic involvement, typically were not offered colonoscopic screening and surveillance and were excluded from the study. During colonoscopy, typically four quadrant biopsies were taken randomly (not targeted) at 10-cm intervals throughout the colon. Novel endoscopic techniques (chromoendoscopy, narrow band imaging (NBI), confocal laser endomicroscopy and autofluorescence) during the screening and surveillance program were not utilized. Additional biopsy specimens were obtained at sites of strictures or raised lesions. Following screening colonoscopy, patients subsequently underwent a follow-up surveillance colonoscopy program in accordance with standard clinical practice guidelines.

2.1. Microscopic classification of dysplasia

Microscopic classification of dysplasia was divided into five categories according to the established criteria by Riddell et al.: negative for dysplasia, indefinite for dysplasia (IND), low-grade dysplasia (LGD), high-grade dysplasia (HGD) or invasive cancer. Two expert GI pathologists reviewed the biopsy specimens. Where there was disagreement, a third GI pathologist was consulted and a consensus was ultimately reached.

2.2. Statistical methods

Continuous variables, i.e. age of disease onset, disease duration (years) and interval between colonoscopic examination (months), were grouped and bivariate analysis for statistically significant association between pathologic findings and variables was assessed utilizing the two-tailed Fisher’s exact and chi-squared tests. A p-value ≤ 0.05 was considered to be statistically significant. Survival analysis curve was done using the Kaplan–Meier estimate. Analysis was
performed in R statistical computing software. The logrank test was used to compare the survival distributions of two samples.

3. Results

3.1. Patient and disease characteristics

A total of 904 screening and surveillance colonoscopies were performed on 411 patients with long-standing Crohn’s colitis, where 50.3% were female (n = 207). The mean number of examinations per patient was 2.2 (range 2–9). The mean age at diagnosis and the disease duration were 26.7 and 19.4 years, respectively (Table 1a). Among patients with neoplasia (n = 23) extensive colitis was found in 43% (n = 10), while isolated right- and left-sided disease were found in 30% (n = 7) and 27% (n = 6), respectively (Table 1b). Three patients who developed colonic neoplasia had a first degree relative with inflammatory bowel disease. In addition, 37% (n = 9) of patients who developed neoplasia had prior partial colonic resection.

Overall 23 patients (5.6%) were found to have neoplasia; 12 patients (2.92%) had IND, 11 patients (2.68%) had LGD, 3 patients (0.73%) had HGD, 3 patients (0.73%) had anal cancer and 6 patients (1.46%) had rectal cancer (Table 2). In 2 of 11 (18%) patients, LGD was detected in raised lesions (DALM) and in the remaining 9 patients dysplasia was detected in flat mucosa. Patients with HGD underwent surgical resection, while 2 patients with LGD later developed HGD and ultimately required surgical resection. Patients with normal examinations had a mean age of 46.2 ± 0.72 years (Table 2). Patients diagnosed with LGD had mean age of 53.6 ± 4.70 years (p = 0.156), while HGD had mean age of 42.0 ± 6.24 years (p = 0.270). Patients with anal cancer had a mean age of 56.3 ± 2.54 years (p = 0.045), while patients with rectal cancer had a mean age of 57.5 ± 7.36 years (p = 0.006). All 3 patients who developed HGD had a prior biopsy demonstrating LGD, confirming a progressive process. All 3 patients underwent surgical resection (segmental resection in 2 and total colectomy with ileostomy in 1). Two of 3 patients who underwent surgical resection for HGD were found to have invasive cancer in addition to HGD on pathology specimens. Meanwhile, patients with LGD subsequently underwent 2 colonoscopic examinations on average over a period of 4 years. Two of 11 patients with LGD reverted to normal pathology on follow-up colonoscopic examinations.

3.2. Age at diagnosis of Crohn’s disease and disease duration

Age at CD diagnosis and disease duration in relation to the histological findings of the screening and surveillance program is shown in Table 2. Patients with normal examinations had a mean age at CD diagnosis of 25.63 ± 0.77 years of age and mean disease duration of 19.13 ± 0.52 years. Patients with HGD were significantly younger at the time of CD diagnosis (17.74 ± 2.69 years; p < 0.001), and had considerably longer disease duration than those without abnormal histological findings (36.82 ± 4.38 years; p < 0.001). In contrast patients with RC and AC were older than those patients with normal histological findings and had longer diseases duration (Table 2). More interestingly, in recent follow up 18% of patients with LGD later developed HGD, demonstrating the importance of timely sequential surveillance colonoscopies. Such evidence is corroborated from data analyzed in Table 3, which shows a progression of lesions as seen during surveillance colonoscopy.

Since younger age of CD onset appears to be a risk factor for the development of dysplasia and cancer, survival analysis was performed using the Kaplan–Meier estimate to further illustrate the relationship between the age of CD onset and the detection of neoplasia in patients undergoing screening and surveillance (Fig. 1). Age ≥ 19 and < 40 years at CD diagnosis were more likely to develop dysplasia and/or carcinoma (p = 0.0866). Patients with later onset of CD had a lower probability of developing dysplasia and/or carcinoma. The risk of developing dysplasia heightened 18 years after CD onset when CD was diagnosed < 40 years of age (Fig. 1).

3.3. Examination frequency and intervals

Patients with normal examinations had a mean of 2.15 ± 0.09 exams per patient with a mean time interval of 12.92 ± 1.25 months between exams (Fig. 2). The LGD group had a mean of 3.63 ± 0.62 colonoscopies per patient (p = 0.03) and a mean time interval of 17.14 ± 2.14 months between exams (p = 0.01). The 3 patients who developed HGD had 2.33 ± 0.427 colonoscopies per patient (p = 0.912) with a mean time interval of 31.54 ± 9.43 months between exams (p = 0.002). Rectal and anal carcinoma had a mean of 3.56 ± 0.38 colonoscopies per patient (p = 0.450) and a mean time interval of 35.38 ± 8.26 months between exams (p = 0.087) (Fig. 2). Seventy-two percent of LGD (n = 8) was diagnosed on initial screening or first surveillance colonoscopy; 27% (n = 3) on screening colonoscopy, and 45% (n = 5) on first surveillance colonoscopy. Interestingly, the majority of carcinomas were detected after the first surveillance examination and only one at the time of the screening colonoscopy (Table 3).
4. Discussion

We report findings of a screening and surveillance program for the largest patient cohort (n=411) with long-standing Crohn’s colitis. The patients were followed using common clinical practice that has been adopted at our IBD Center rather than using a set research protocol. Several studies have reported an increased risk of cancer in IBD. We detected neoplasia in 5.6% of our patient population. The incidence of dysplasia and cancer was substantially lower in our study population (1.21% on screening and 4.38% on surveillance examinations) than the one reported by Friedman et al. (7% on screening and 14% on surveillance examinations). Overall, we detected cancer in 2.19% of our patient population, which is lower than that reported by Gillen et al. (8% at 22 years). These observations were most likely secondary to a lower frequency of extensive colitis in our patient cohort, which was 55% of our population, compared to 90% and 100% in the two aforementioned studies, respectively. The extent of inflammation appears to be a risk factor for CRC, as patients with pancolitis generally develop CRC a decade prior to IBD patients with left-sided disease. Nonetheless, it appears that patients with Crohn’s colitis have a significantly increased risk for developing CRC—up to an 18-fold risk in extensive colitis—and those with significant colitis may have an incidence of neoplasia comparable to those reported for chronic ulcerative colitis (13%).

The frequency and interval of examinations may have influenced the detection of dysplasia and cancer. Patients who developed HGD had a significantly longer interval between examinations (31.54 months) than patients with normal examinations. Most dysplasia was reported in the first two examinations, only one of the cases of malignancy was diagnosed in the first two colonoscopies. This data supports a role for increased vigilance and long-term surveillance of CRC in CD with colonic involvement.

Patients with malignancy diagnosed on colonoscopy were significantly older at the time of examination than those with normal examinations, supporting the established correlation between increased age and risk for CRC. These data suggest that additional factors may contribute to colorectal cancer risk related to individual inherited, geographic, or other environmental factors. Although age at the time of examination may have been a significant and important factor, age at diagnosis and disease duration may be more important. Patients who developed HGD and cancer were significantly younger at the time of CD diagnosis and had approximately twice the disease duration (37-45 years) compared to patients with normal examinations (19 years). Such evidence corroborates reports that age of CD onset and CD duration are risk factors for CRC development.

Although there appears to be a strong correlation between IBD and colorectal cancer, the ultimate utility of screening and surveillance colonoscopy has been controversial. A number of investigators have highlighted the need

### Table 2

<table>
<thead>
<tr>
<th>Histology</th>
<th>n</th>
<th>Age at diagnosis (y)</th>
<th>Age (y)</th>
<th>Duration of disease (y)</th>
<th>Mean colonoscopies per subject</th>
<th>Duration of surveillance (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>376</td>
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<td>46.2</td>
<td>19.13</td>
<td>2.15</td>
<td>11.64</td>
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<td>LGD</td>
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<td>36.85</td>
<td>53.64</td>
<td>16.88</td>
<td>3.63</td>
<td>12.23</td>
</tr>
<tr>
<td>HGD</td>
<td>3</td>
<td>17.74*</td>
<td>42</td>
<td>36.82*</td>
<td>2.33</td>
<td>9.45</td>
</tr>
<tr>
<td>RC</td>
<td>6</td>
<td>22.86</td>
<td>57.52*</td>
<td>35</td>
<td>3.5</td>
<td>26.71</td>
</tr>
<tr>
<td>AC</td>
<td>3</td>
<td>18.45</td>
<td>56.32*</td>
<td>45.13</td>
<td>3.66</td>
<td>32.38</td>
</tr>
</tbody>
</table>

*y = years; LGD = low-grade dysplasia; HGD = high-grade dysplasia; RC = rectal carcinoma; AC = anal carcinoma. (*) Indicates a statistically significant difference compared to normal examinations.

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>LGD</th>
<th>HGD</th>
<th>CA</th>
<th>Total*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>3</td>
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<td>1</td>
<td>22%</td>
</tr>
<tr>
<td>Surveillance</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>22%</td>
</tr>
<tr>
<td>1st</td>
<td>1</td>
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<td>2</td>
<td>12%</td>
</tr>
<tr>
<td>2nd</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>26%</td>
</tr>
<tr>
<td>3rd</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>9%</td>
</tr>
</tbody>
</table>

LGD = low-grade dysplasia; HGD = high-grade dysplasia; CA = carcinoma. *represents percentage among the 23 patients with neoplasia detected during screening and surveillance examinations.

![Figure 1](https://academic.oup.com/ecco-jcc/article-abstract/6/8/824/370085/fig1)

Kaplan–Meier estimate of neoplasia-free survival in the Crohn’s colitis cohort in different age-groups.
for secondary prevention.\textsuperscript{11,39,40} Furthermore, a 2006 Cochrane Database review reported detection of cancers at an earlier stage and better prognosis in patients undergoing surveillance.\textsuperscript{47} However, the authors concluded that “there is no clear evidence that surveillance colonoscopy prolongs survival in patients with extensive colitis.” Nevertheless, there is indirect evidence that surveillance may be cost-effective and in fact reduces the risk of death from IBD-associated CRC. A recent study indicated that having a colonoscopy for an indication of surveillance or screening is associated with decreased risk of CRC in the setting of Crohn’s colitis.\textsuperscript{42}

The most recent guidelines from the Crohn’s and Colitis Foundation of America (CCFA) recommend screening colonoscopy 8–10 years after the onset CD disease involving at least one-third of the colon.\textsuperscript{13} The recommended time to initiate screening appears appropriate based on our data, as the shortest mean disease duration to diagnosis of dysplasia or cancer was approximately 17 years (LGD).

If screening colonoscopy is negative for dysplasia, surveillance examination is recommended every 1–2 years thereafter. Patients with normal colonoscopies in our study population had a mean interval between examinations of 13 months, and the mean interval for the detection of biopsy findings in low-grade dysplasia (17 months) also fell into this range. The interval of exams in patients with HGD (31 months) and cancer (35 months) was significantly longer than the normal group and beyond the CCFA guidelines discussed above, supporting a recommendation of surveillance examination every 1–2 years in patients with Crohn’s colitis. Whether the utilization of chromoendoscopy or other novel endoscopic techniques (NBI, autofluorescence) may enhance detection of dysplasia in Crohn’s colitis surveillance programs need to be evaluated in large prospective trials.

In conclusion, dysplasia and cancer were detected in a lower proportion of patients with colonic involvement of CD compared with a previous study, which may have been attributed to a lower proportion of patients with extensive colitis, a well-known risk factor for CRC in IBD. Moreover, the utilization of surveillance colonoscopy as standard of care was only recently adopted; therefore a greater incidence of neoplasia may be detected in future studies. We report that earlier age at the time of diagnosis, longer disease duration and increased interval between examinations were associated with biopsy findings of HGD and cancer. Further studies are necessary to prospectively assess the risk of CRC in CD.

**Conflict of interest**

The authors declare that there is no potential conflict of interest related to this article.

**References**