High Risk of Advanced Colorectal Neoplasia in Patients With Primary Sclerosing Cholangitis Associated With Inflammatory Bowel Disease

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BACKGROUND & AIMS: **Patients with inflammatory bowel disease (IBD) and primary sclerosing cholangitis (PSC, termed PSC-IBD) are at increased risk for colorectal cancer, but their risk following a diagnosis of low-grade dysplasia (LGD) is not well described. We aimed to determine the rate of advanced colorectal neoplasia (aCRN), defined as high-grade dysplasia and/or colorectal cancer, following a diagnosis of indefinite dysplasia or LGD in this population.**

METHODS: **We performed a retrospective, longitudinal study of 1911 patients with colonic IBD (293 with PSC and 1618 without PSC) who underwent more than 2 surveillance colonoscopies from 2000 through 2015 in The Netherlands or the United States (9265 patient-years of follow-up evaluation). We collected data on clinical and demographic features of patients, as well as data from each surveillance colonoscopy and histologic report. For each surveillance colonoscopy, the severity of active inflammation was documented. The primary outcome was a diagnosis of aCRN during follow-up evaluation. We also investigated factors associated with aCRN in patients with or without a prior diagnosis of indefinite dysplasia or LGD.**

RESULTS: **Patients with PSC-IBD had a 2-fold higher risk of developing aCRN than patients with IBD only. Mean inflammation scores did not differ significantly between patients with PSC-IBD (0.55) vs patients with only IBD (0.56) ($P = .89$), nor did proportions of patients with LGD (21% of patients with PSC-IBD vs 18% of patients with only IBD) differ significantly ($P = .37$). However, the rate of aCRN following a diagnosis of LGD was significantly higher in patients with PSC-IBD (8.4 per 100 patient-years) than patients with only IBD (3.0 per 100 patient-years; $P = .01$). PSC (adjusted hazard ratio [aHR], 2.01; 95% CI, 1.09–3.71), increasing age (aHR 1.03; 95% CI, 1.01–1.05), and active inflammation (aHR, 2.39; 95% CI, 1.63–3.49) were independent risk factors for aCRN. Dysplasia was more often endoscopically invisible in patients with PSC-IBD than in patients with only IBD.**

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Abbreviations used in this paper: aCRN, advanced colorectal neoplasia; aHR, adjusted hazard ratio; CRC, colorectal cancer; EHR, electronic health record; HGD, high-grade dysplasia; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease undifferentiated; IND, indefinite dysplasia; LGD, low-grade dysplasia; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

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CONCLUSIONS: **In a longitudinal study of almost 2000 patients with colonic IBD, PSC remained a strong independent risk factor for aCRN. Once LGD is detected, aCRN develops at a higher rate in patients with PSC and is more often endoscopically invisible than in patients with only IBD. Our findings support recommendations for careful annual colonoscopic surveillance for patients with IBD and PSC, and consideration of colectomy once LGD is detected.**

Keywords: Surveillance; Colon Cancer; Crohn's Disease; Ulcerative Colitis.

Patients with inflammatory bowel disease (IBD) are at an increased risk of developing colorectal cancer (CRC).[1,2] The co-occurrence of primary sclerosing cholangitis (PSC),[1,3] a chronic liver disease characterized by progressive inflammation and fibrosis of the bile ducts,[4] increases this risk substantially.[5] Although an estimated 70% of patients with PSC have a concomitant diagnosis of IBD (termed PSC-IBD),[6] only 3% to 5% of patients with IBD have concomitant PSC, with the diagnosis more common in patients with ulcerative colitis (UC).[5,7] The PSC-IBD phenotype often is characterized by extensive colitis with rectal-sparing and backwash ileitis, albeit with a mild and often asymptomatic clinical course.[8–13] However, despite their mild clinical colitis, patients with PSC-IBD compared with patients with only IBD colitis have a 3- to 5-fold higher risk of CRC, and the cancers occur more often in the right colon.[14,15] As such, current guidelines recommend that patients with PSC-IBD be enrolled in a CRC surveillance program with an annual colonoscopy from the time of PSC diagnosis, regardless of their duration of IBD. This is in contrast to patients with IBD colitis and no PSC (non-PSC IBD), in which CRC surveillance is recommended after 8 years of colonic disease.[5,16–18]

The development of neoplasia in IBD colitis follows a multistep sequence from chronic inflammation and no dysplasia or indefinite dysplasia (IND) to low grade-dysplasia (LGD) and high-grade dysplasia (HGD), before final malignant transformation to adenocarcinoma. As such, the presence and grade of dysplasia remain the best current indicators of cancer risk in IBD. There is an increasing tendency to keep patients with LGD on intensive surveillance instead of recommending proctocolectomy.[19,20] However, very few studies have described the risk of advanced colorectal neoplasia (aCRN) in patients with PSC-IBD after a diagnosis of IND and/or LGD.[21,22] Furthermore, the studies that do report on the risk of neoplasia in patients with PSC-IBD were performed in an era in which imaging-enhanced endoscopy and high-resolution endoscopy were not used routinely.

The aims of the present study were to report on the risk of aCRN in a well-characterized cohort of patients with PSC-IBD enrolled in a surveillance program in the modern endoscopic era, and to describe the rate of aCRN after a diagnosis of IND and/or LGD in these patients compared with patients with non-PSC IBD and long-standing IBD colitis also undergoing surveillance.

Methods

Study Population and Case Identification

Patients with established IBD colitis undergoing colonoscopic surveillance between 2000 and 2015 were identified retrospectively from 2 databases: a Dutch database inclusive of 2 secondary and 6 tertiary centers and the Mount Sinai Hospital database in New York City inclusive of 1 tertiary IBD referral center. Cases were identified by query of the electronic health record (EHR)-linked database using both International Classification of Diseases, 9th and 10th revision codes, and free text searches for cases of IBD and also free text searches for PSC.

Patient Selection: Inclusion and Exclusion Criteria

After initial identification through the EHR query, individual charts were reviewed. For patients with PSC-IBD, a clinical diagnosis of PSC had to be confirmed by distinctive features on cholangiography or liver biopsy (for patients with small-duct PSC). Additional inclusion criteria were as follows: (1) diagnosis of IBD (UC, CD, IBD undifferentiated [IBD-U]) with colonic involvement confirmed endoscopically and histologically; (2) confirmed colonic disease duration of at least 8 years for patients with non-PSC IBD or any colonic disease duration for patients with PSC-IBD; (3) enrollment in a surveillance program; and (4) at least left-sided colitis (UC or IBD-U) or involvement of more than 30% of the colonic surface (CD or IBD-U). Patients with a history of colectomy before enrollment or a history of aCRN before or at the index colonoscopy during the defined study period were excluded. Surveillance procedures were defined as colonoscopies in which either segmental random biopsies or chromoendoscopy were used. Colonoscopies with other indications (eg, medically refractory disease), were excluded. The index colonoscopy was defined as the first surveillance colonoscopy performed within the study period (2000–2015).

Data Collection

Database coding was identical for all study populations. The date of study entry was set at the first surveillance colonoscopy in the database. The time of