More Right-sided IBD-associated Colorectal Cancer in Patients with Primary Sclerosing Cholangitis

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Background: Patients with inflammatory bowel disease (IBD) and concurrent primary sclerosing cholangitis (PSC) have a higher risk of developing colorectal cancer (CRC) than IBD patients without PSC. The aim of this study was to investigate potential clinical differences between patients with CRC in IBD and those with CRC in IBD and PSC, as this may lead to improved knowledge of underlying pathophysiological mechanisms of CRC development.

Methods: The retrospective study from 1980–2006 involved 7 Dutch university medical centers. Clinical data were retrieved from cases identified using the national pathology database (PALGA).

Results: In total, 27 IBD-CRC patients with PSC (70% male) and 127 IBD-CRC patients without PSC (59% male) were included. CRC-related mortality was not different between groups (30% versus 19%, $P = 0.32$); however, survival for cases with PSC after diagnosing CRC was lower (5-year survival: 40% versus 75% for PSC group). Right-sided tumors were more prevalent in the PSC group (67% versus 36%, $P = 0.006$); adjusted for age, sex, and extent of IBD, this difference remained significant (odds ratio: 4.8, 95% confidence interval [CI] 2.0–11.8). In addition, tumors in individuals with PSC were significantly more advanced.

Conclusions: The right colon is the predilection site for development of colonic malignancies in patients with PSC and IBD. When such patients are diagnosed with cancer they tend to have more advanced tumors than patients with IBD without concurrent PSC, and the overall prognosis is worse. Furthermore, the higher frequency of right-sided tumors in patients with PSC suggests a different pathogenesis between patients with PSC and IBD and those with IBD alone.

Key Words: colorectal cancer, primary sclerosing cholangitis, inflammatory bowel disease
PSC and IBD and guide future research in pathophysiological mechanisms in PSC–IBD-associated CRC.

MATERIALS AND METHODS

Patients

The Dutch nationwide network and registry of histopathology reports (PALGA) was used to select patients with PSC-IBD-associated CRC.12 A search in this database from January 1990 until June 2006 for cases diagnosed, in Dutch university medical centers, with synchronous or metachronous diagnoses of IBD and CRC was performed.13 Patients with PSC-IBD and CRC were also selected from this search and from a long-term cohort study containing all PSC patients followed in the period 1980–2006 in 2 university medical centers (University Medical Center Utrecht and Erasmus Medical Center Rotterdam).8

The diagnosis PSC was based on typical findings on cholangiography14 or the presence of characteristic histological liver abnormalities (pericholangiolar “onion-skin” fibrosis), in combination with elevated serum alkaline phosphatase levels and the presence of IBD.15 The onset of PSC was designated as the date of the first abnormalities on cholangiography or liver histology. Patients with bile duct abnormalities attributable to other causes such as bile duct surgery, ischemia, portal vein thrombosis, or autoimmune pancreatitis were excluded.

The diagnoses IBD and CRC were based on a combination of endoscopic and histological findings.16 Patients with mere dysplasia were not eligible. Colonic surveillance was based on the American Gastroenterological Association (AGA) or British Society of Gastroenterology (BSG) guidelines and defined as surveillance after 8–10 years of disease (AGA) or British Society of Gastroenterology (BSG) guidelines and defined as surveillance after 8–10 years of disease or after diagnosing CRC.

Clinical Characteristics

Data Collection

Data were retrieved from medical records and computerized hospital databases and completed by contacting the patient’s physician. Collected data included date of diagnosis of IBD, PSC, and CRC, time of onset of symptoms, medical history, location and stage of the CRC, cause of death, use of 5-aminosalicylic acid (5-ASA) and/or ursodeoxycholic acid (UCDA), and information on phenotype of IBD (extent, duration, and type). Extensive colitis was defined as a colitis proximal of the splenic flexure in patients with UC or >50% involved colonic mucosa in patients with CD. End of follow-up was the end of the study (June 2006), death, or time of last visit in case patients were lost to follow-up. Apart from location and stage of the CRC, information on synchronous and metachronous tumors was collected as well. Right-sided or proximal tumors were defined as tumors located proximally of the splenic flexure. Tumor stages were defined according to the American Joint Committee on Cancer (AJCC).19

Statistical Analysis

Follow-up started at the time when CRC was diagnosed. Differences between patients with PSC and IBD and those with IBD alone were analyzed using Student’s t-test and the chi-square test, when appropriate. A separate analysis was performed, excluding the patients with CD to rule out that possible differences were based on the underlying type of IBD. Multivariate analysis was done using binary logistic regression to determine whether there were independent risk factors for tumor location. These variables included age at diagnosis CRC, gender, presence of PSC, and extent of colitis. Survival analyses were performed using the Kaplan–Meier method; differences between groups were analyzed with the log-rank test. SPSS 12.0 Statistical Software (Chicago, IL) was used for all statistical analyses. The Kaplan–Meier plots were created in MedCalc for Windows, v. 9.3. (MedCalc Software, Mariakerke, Belgium). P-values < 0.05 were considered statistically significant.

RESULTS

Clinical Characteristics

Twenty-seven IBD-CRC patients with PSC (70% male) and 127 IBD-CRC patients without PSC (59% male) were included. Median age at diagnosis of IBD was 33 years (range 3–46) and 28 years (range 6–82) in the groups with and without concurrent PSC, respectively (P = 0.5) (Table 1). Median age at diagnosis of PSC was 39 years (range 11–59). The majority of patients had extensive colitis, i.e., 89% and 71% of patients with and without PSC, respectively (P = 0.1). UC was diagnosed in 89% of the patients with PSC, and in 56% of the patients without PSC (P = 0.003). All patients with CD had colonic involvement; an extensive colitis (>50% inflammation) was found in 100% and 63% of the patients with and without PSC, respectively. Sixty-nine percent (n = 31) of the non-PSC patients with CD also had ileitis compared to 33% (n = 1) of the CD patients in the PSC group. The majority (86%) of all patients used 5-ASA. UCDA was used by 15 PSC patients (56%) and by 1 patient without PSC. The latter patient used it for cholelithiasis.

After excluding all patients with CD, 24 UC-CRC patients with PSC (67% male) and 72 UC-CRC patients without PSC (67% male) remained. No changes in age at diagnosis IBD or PSC were found. Almost all patients in the PSC-UC-CRC group had an extensive colitis (92%) compared to 79% in the UC-CRC group (P = 0.2).

Follow-up

The median follow-up period after diagnosing CRC was 2.3 years (range 0–17.3) and 2.7 years (0–19.5) for the
TABLE 1. Patient Characteristics of 27 PSC-IBD-CRC Patients and 127 IBD-CRC Patients

<table>
<thead>
<tr>
<th></th>
<th>PSC-IBD-CRC (n = 27)</th>
<th>IBD-CRC (n = 127)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, (% male)</td>
<td>19 (70)</td>
<td>75 (59)</td>
<td>0.4</td>
</tr>
<tr>
<td>Median age at diagnosis IBD, yrs (range)</td>
<td>33 (3–46)</td>
<td>28 (6–82)</td>
<td>0.5</td>
</tr>
<tr>
<td>Median age at diagnosis PSC, yrs (range)</td>
<td>39 (11–59)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Median age at diagnosis CRC, yrs (range)</td>
<td>47 (27–67)</td>
<td>49 (20–84)</td>
<td>0.06</td>
</tr>
<tr>
<td>Maximal extent of IBD (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extensive</td>
<td>24 (89)</td>
<td>80 (71)</td>
<td>0.1</td>
</tr>
<tr>
<td>Type of IBD (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ulcerative colitis</td>
<td>24 (89)</td>
<td>71 (56)</td>
<td>0.003</td>
</tr>
<tr>
<td>- Crohn’s disease</td>
<td>3 (11)</td>
<td>55 (43)</td>
<td></td>
</tr>
<tr>
<td>Median IBD-CRC interval, yrs (range)</td>
<td>13 (0–35)</td>
<td>17 (0–43)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

PSC, primary sclerosing cholangitis; IBD, inflammatory bowel disease; CRC, colorectal cancer. NA: not applicable.

PSC and non-PSC group, respectively (P = 0.09). Sixty percent (n = 16) of the patients in the PSC group died versus 25% (n = 32) in the non-PSC group (P = 0.002). CRC-related mortality was not different between the 2 groups, i.e., 30% and 19% in the PSC-IBD-CRC and IBD-CRC group (P = 0.324). Other causes of death are shown in Table 2. Twenty-one percent of all patients were lost to follow-up. Differences in mortality rates remained statistically significant after excluding the CD patients (63% and 23% in the PSC-UC-CRC patients and UC-CRC patients, respectively).

TABLE 2. Causes of Death in 16 PSC-IBD-CRC Patients and 32 IBD-CRC Patients

<table>
<thead>
<tr>
<th></th>
<th>PSC-IBD-CRC n = 16</th>
<th>IBD-CRC n = 32</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal carcinoma</td>
<td>8 (50)</td>
<td>24 (75)</td>
<td></td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>2 (13)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Other malignancy</td>
<td>0 (0)</td>
<td>3 (9)</td>
<td></td>
</tr>
<tr>
<td>Colectomy</td>
<td>2 (13)</td>
<td>3 (9)</td>
<td></td>
</tr>
<tr>
<td>Liver failure</td>
<td>1 (6)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Other causes</td>
<td>1a (6)</td>
<td>2a (6)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (13)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

aGastric, urothelial, and renal cell cancer.

In the PSC_UC_CRC group 47% of the deaths were CRC-related versus 81% in the UC_CRC group (P = 0.044).

Three patients with PSC had undergone liver transplantation before developing CRC. These patients were not enrolled in a surveillance program, but underwent colonoscopy at an irregular basis without taking the required number of biopsies. The median interval between liver transplantation and detection of CRC was 13 months (range 2–20). Liver transplantation following a prior diagnosis of CRC was not performed.

The estimated overall 5-year survival rate after the diagnosis CRC was lower for patients with PSC (40%) than for those without PSC (75%, P ≤ 0.001) (Fig. 1a,b). CRC-related mortality was not statistically significant different, with a 5-year survival of 62% and 82% for patients with and without PSC, respectively (P = 0.1) (Fig. 2a,b).

Colorectal Carcinoma

Patients were younger at CRC diagnosis in the PSC group than in the non-PSC group (median age: 47 years (range 27–67) versus 49 years (range 20–84, P = 0.064)). The median interval between the diagnosis IBD and the development of CRC was not different, i.e., 13 years (range 0–35) in the PSC group and 18 years (range 0–43) in the non-PSC group (P = 0.2). Patients with PSC had significantly more tumors with an AJCC tumor stage of 3A or higher compared to patients with IBD alone (61.5% and 38.5%, P = 0.003) (Table 3). Eleven patients (9%) in the non-PSC group had a synchronous CRC and 3 (2.4%) patients had 3 tumors diagnosed at the same time. Synchronous tumors were not detected in the PSC group. No statistically significant differences were found in the AJCC tumor stages when comparing PSC_UC_CRC to UC_CRC patients (tumor stage of 3A or more: 61% of the PSC_UC_CRC patients and in 41% of the UC_CRC patients, respectively, P = 0.091).

The tumors were located proximally of the splenic flexure in 18 (67%) patients with PSC and in 52 (36%) patients without PSC (P = 0.006). After excluding patients with CD, this difference remained statistically significant (P = 0.02). Multivariate analysis, including age at diagnosis of CRC, gender, and extent of colitis showed that PSC was an independent risk factor for (right-sided) tumor location with an odds ratio of 4.8 (95% confidence interval [CI] 2.0–11.8).

Only a small number of patients underwent colonic surveillance according to the AGA/BSG guidelines, i.e., 33% and 17% patients with and without PSC, respectively. No difference in AJCC tumor stage was found between patients with or without colonic surveillance (P = 0.128).

DISCUSSION

This study shows a significantly higher prevalence of right-sided CRCs in patients with PSC and IBD compared to patients with IBD alone. These findings are in line with
results from previous series. However, the studies of Marchesa et al.,20 Lindberg et al.,21 and Shetty et al.10 were all based on relatively small numbers of CRC patients with IBD with or without concomitant PSC. In addition, we found that CRC in patients with PSC and IBD was associated with a decreased survival compared to patients with IBD alone. The difference in CRC-related 5-year survival (62% versus 82%) between the 2 groups, however, was not statistically significant.

The high frequency of right-sided colorectal tumors in PSC patients fits well with the hypothesis that an altered bile acid composition is implicated in the increased frequency of CRCs in these patients.10 In this respect, an increased concentration of secondary bile acids and higher serum and bile levels of deoxycholic acid and lithocholic acid both might play a role.22–24 Interestingly, specific binding sites for deoxycholic acid were identified in 31% of the sporadic CRCs compared to only 3% of normal mucosa samples (P

FIGURE 1. Kaplan–Meier plot of survival (+95% CI) after diagnosing CRC of 27 patients with PSC and concurrent IBD (a) and 127 patients with IBD alone (b) (P = 0.002, log-rank test).

FIGURE 2. Kaplan–Meier plot of the CRC-related mortality (+95% CI) for 27 patients with PSC and concurrent IBD (a) and 127 patients with IBD alone (b) (P = 0.324, log-rank test).
The same has been observed in colitis-associated carcinogenesis by Hill et al., who reported an increased concentration of total fecal bile acids in UC patients with dysplasia or carcinoma as well. The promising results of UDCA as a chemoprotective agent in the development of CRC in UC patients with concurrent PSC also suggest a role for bile acids in colorectal carcinogenesis. On the other hand, the sparse data available on bile composition in patients with PSC do not corroborate this hypothesis: bile acid excretion in cholestatic patients, including PSC patients, is decreased and serum concentration of secondary bile acids was not increased in patients with PSC when compared to healthy controls. In addition, the risk of developing CRC remains increased after liver transplantation, which is likely to normalize bile acid composition.

Another explanation for the predominance of right-sided CRCs in PSC may be offered by an alternative molecular pathogenesis. A parallel might be drawn with patients with hereditary nonpolyposis colon cancer (HNPCC) in whom a high frequency of right-sided tumors occurring at a relatively young age is observed as well. The pathophysiological mechanism of this hereditary disease is based on a defect in the DNA mismatch repair genes. In colitis-associated carcinogenesis, data regarding defects in DNA mismatch repair genes and the associated molecular phenotype of microsatellite instability (MSI) are conflicting. The frequency of MSI varies between 1% and 45%, depending on the types of tissue analyzed and, in particular, the number and choice of microsatellite markers. The frequency of MSI in patients with IBD-associated CRC and concurrent PSC is presently unknown.

A remarkable observation of our study was that the IBD-CRC interval between patients with and without PSC did not differ. Although PSC is known to be an additional risk factor for CRC, our results do not support an accelerated progression to CRC in these patients. However, as many PSC patients seem to have asymptomatic or mild colitis, the exact date of onset of IBD is difficult to establish. This might have led to an underestimation of the duration of the colitis.

A minority of patients (20%) were enrolled in a strict surveillance colonoscopy program. During the 1980s and 1990s, the currently accepted guidelines were not yet implemented, which might explain this low percentage. In addition, the fact that 3 patients developed CRC relatively soon after liver transplantation also illustrates that the current standard of surveillance before and after liver transplantation was not yet introduced at that time.

Patients with PSC had a decreased survival in comparison with the non-PSC group, although CRC-related mortality did not differ. Most patients in both groups died from CRC. Although statistically not significant, the difference in the 5-year survival rate of 62% and 82% for CRC patients with and without PSC, respectively, is noteworthy. The observed higher frequency of more advanced AJCC tumor stages in the PSC group may explain this lower survival rate. The lack of significance may be ascribed to the relatively small patient population (type II error).

Several limitations of this study are worth considering. First of all, data were collected retrospectively. Second, the controls were not case-matched. Due to the asymptomatic course of IBD in patients with PSC it is difficult to match patients with regard to IBD duration and extent. In the multivariate analysis we corrected for the extent of the colitis as a potential confounder. Finally, in the IBD-CRC group more patients with CD were included compared to the PSC-CRC group, which may have affected the results. However, all patients with CD had colonic involvement and after excluding the patients with CD from analysis the differences remained statistically significant.

In summary, our study shows that CRCs develop predominantly in the proximal colon of PSC patients with IBD. Additional studies are needed to explore the underlying molecular mechanisms to explain these findings.

ACKNOWLEDGMENT
The authors thank Dr. M. Casparie (Prismant, Utrecht, the Netherlands) for help with the PALGA data search.

REFERENCES


