Digestive and Liver Disease 51 (2019) 1257–1264

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

Difference in the clinical characteristic and prognosis of colitis-associated cancer and sporadic neoplasia in ulcerative colitis patients

Makoto Mutaguchi[a,*], Makoto Naganuma[a,*], Shinya Sugimoto[a], Tomohiro Fukuda[a], Kosaku Nanki[a], Shinta Mizuno[a], Naoki Hosoe[b], Masayuki Shimoda[c], Haruhiko Ogata[b], Yasushi Iwao[d], Takanori Kanai[a,*]

[a] Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan
[b] Center for Diagnostic and Therapeutic Endoscopy, Keio University School of Medicine, Tokyo, Japan
[c] Department of Pathology, Keio University School of Medicine, Tokyo, Japan
[d] Center for Preventive Medicine, Keio University School of Medicine, Tokyo, Japan

ARTICLE INFO

Article history:
Received 31 October 2018
Accepted 2 May 2019

Keywords:
Ulcerative colitis
Colitis-Associated dysplasia
Adenoma-Like dysplasia
Colorectal cancer

ABSTRACT

Background: Although various studies have been conducted on colitis-associated cancer (CAC), few have assessed the differences in the clinical and endoscopic features, treatment, and prognosis of CAC and sporadic neoplasia (SN) in the inflamed mucosa of ulcerative colitis (UC) patients.
Aims: To compare the characteristics of CAC and SN within the previously or currently inflamed mucosa.
Methods: Between 1997 and 2017, we retrospectively analyzed the endoscopic chart data of 348 colonic lesions from 266 UC patients. Non-dysplastic lesions and lesions located outside the inflamed mucosa were excluded. The diagnosis of CAC or SN was confirmed by conventional histopathological and immunohistochemical evaluation of p53 and Ki67.
Results: In total, 74 patients with CAC (97 lesions) and 46 with SN (58) were enrolled. The proportions of patients with a younger age of onset of UC, with chronic persistent UC, and with severe inflamed mucosa were significantly higher in the CAC group. In the SN group, no flat lesions were found, whereas 26% of the lesions in the CAC group were flat. Sixteen patients died during a median follow-up of 6.1 years (interquartile range (IQR) 1.8–11.1)in the CAC group, whereas 1 patient died during a median follow-up 3.2 years(IQR 1.4–4.6) in the SN group. Mortality from colorectal cancer was significantly higher (P = 0.015) in the CAC group (12/68; 17.6%) than in the SN group (1/44; 2.3%). The 5-year survival rate was 100% in the SN group and 97% in the CAC group for lesions located in the mucosa or submucosa.
Conclusion: Recognizing differences in the characteristics of CAC and SN within the inflamed mucosa is critical to avoid unnecessary total colectomy in patients with SN.

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease. Its pathogenesis involves host genetic factors, immune system dysregulation, and environmental factors. Because of recent advances in the treatment of UC, the proportion of patients achieving clinical and endoscopic remission has increased. However, chronic inflammation persists in some patients even after treatment. It has been reported that the chronic inflammation in UC increases the risk of developing colonic dysplasia and cancer [1,2]. Risk factors of colitis-associated cancer (CAC) include extensive colitis [3], primary sclerosing cholangitis [4,5], chronic inflammation with histological activity [6], luminal stenosis or pseudopolyps, [7] and a family history of colorectal cancer [5]. Early detection of CAC is critical for curative treatment; however, detection is challenging against the complex background of the inflamed mucosa of UC patients.

Surveillance colonoscopy is useful for the detection of CAC in the early stages. It has been shown that early diagnosis of patients with CAC using surveillance colonoscopy leads to lower mortality rates [8]. Surveillance colonoscopy frequently detects sporadic ade-

* Corresponding authors at: Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan.
E-mail addresses: nagamakoto@keio.jp (M. Naganuma), takagast@z2.keio.jp (T. Kanai).

https://doi.org/10.1016/j.dld.2019.05.003
1590-8658/

noma and cancer, which are less closely related to inflammation. Although, the incidence of CAC is increased in cases with longer disease duration, the development of sporadic neoplasia (SN) in patients with UC should also be recognized. It is important to understand the differences in the clinical, endoscopic, and pathological characteristics of SN because its management differs from that of CAC. Although various studies were conducted on CAC, there have been few clinical studies on SN associated with UC [9,10]. Furthermore, there are no studies comparing the characteristics of SNs in the previously inflamed mucosa of UC patients to those of CAC.

The aim of this study was to compare the clinical and endoscopic features, treatment method, and prognosis of SN and CAC in UC patients.

2. Material and methods

2.1. Patients

We reviewed the medical charts of 266 consecutive UC patients with 348 lesions (polypoid, adenoma, dysplasia, and cancer) that were endoscopically and/or surgically resected at the Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University Hospital (Tokyo, Japan) between January 1997 and March 2017. Sessile serrated adenomas/polyps (SSA/P), neuroendocrine tumors (NET), and non-dysplastic lesions, including hyperplastic, juvenile, and inflammatory polyps, were excluded from the analyses. Sporadic adenomas and cancers that were located in the colonic mucosa outside the previously or currently inflamed mucosa were excluded from the analyses as they would have detracted from the primary aim of the study. Furthermore, we excluded SNs (<5 mm in size) that were only diagnosed using biopsied specimens without endoscopic resection. Previously reported cases of patients with CAC/high grade dysplasia (HGD) at our institution were included [11]. Subsequently, all lesions were classified into SN and CAC groups and detailed analyses were performed.

2.2. Colonoscopy procedure

Endoscopists observed the entire colon using conventional white-light imaging (WLI). When neoplastic lesions were recognized, indigo-carmine dye was sprayed in some cases to identify the border of the neoplastic lesions. For intraepithelial or submucosal lesions (HGD or submucosal invasive carcinoma), the lesions were classified into 5 categories based on endoscopic findings: (i) pedunculated, (ii) sessile, (iii) superficial elevated, (iv) flat, and (v) depressed lesions, according to the SCENIC (Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations) consensus statement [12]. Mayo endoscopic scores were assessed by an expert in endoscopy for IBD (M.N personally performs the 500 annual endoscopies for IBD patients at our institution). In our surveillance colonoscopies for the detection of CAC, random biopsies were not performed. All included lesions that could not be easily detected by conventional white light imaging were subsequently recognized using chromoendoscopy and/or magnifying endoscopy.

2.3. Histological assessment

All specimens were fixed in 10% formalin and embedded in paraffin. Standard protocols for sectioning paraffin-embedded tissues and hematoxylin and eosin staining were used. At our institution, histological specimens were reviewed and confirmed by at least 2 experienced pathologists. We collected neoplastic lesions, including adenocarcinoma, HGD, low-grade dysplasia (LGD), indefinite dysplasia, serrated adenoma, and tubular adenoma. We excluded patients with LGD and indefinite dysplasia that disappeared during the follow-up period. Adenocarcinoma was classified into well differentiated, moderately differentiated, poorly differentiated, and mucinous. Poor prognostic pathological findings were defined as the presence of poorly differentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous carcinoma. Sporadic adenoma and cancers were defined according to the previous histological criteria [9]. To distinguish CAC lesions from SN lesions, immunohistochemical assessment for p53 and Ki67 were also conducted. According to previous reports [11,13–15], lesions with over-expression or complete absence of p53, or strong and diffuse expression of Ki67 were classified into the CAC group, whereas those with Ki67 expressed preponderantly at the luminal aspect of the elevated lesions with low levels of p53 were classified into the SN group. We also assumed that p53 would be over-expressed in the lesions surrounding CAC, whereas few p53 positive cells would be found around SN. We excluded patients who could not be classified as either CAC or SN by pathologists. The final pathological diagnosis was based on histological assessment of the entire endoscopically or surgically resected lesions. As an exception, histological assessment was performed using biopsy samples from 6 patients of that CAC group that did not undergo resection due to disseminated advanced carcinoma.

2.4. Data collection

Clinical information was retrospectively obtained from medical charts. Sex, distribution of disease (total colitis, left-side colitis, and others), disease type (relapsing and remitting, and chronic continuous), age, age at the onset of disease, and duration of disease were collected. Chronic continuous UC was defined as clinical symptoms of UC that continued for more than 6 months. Clinical remission was defined as a partial Mayo score of ≤ 1 [16]. For endoscopic findings, distribution of neoplastic lesions, number of lesions, and Mayo endoscopic scores were collected when SN or CAC lesions were detected.

For intraepithelial lesions, the morphological classification was assessed according to the classification of the SCENIC international consensus statement [12]. Information on treatment (endoscopic mucosal resection [EMR], endoscopic submucosal dissection [ESD], surgical treatment, or chemotherapy) and prognosis (death due to neoplastic lesions) was also collected.

2.5. Study endpoints and statistical assessment

In this study, we mainly investigated the differences in the clinical, endoscopic, and histological features, treatment, and prognosis between the patients with CAC and those with SN. Categorical variables were compared using the Chi-squared test or Fisher's exact test. Continuous variables were compared using Student's *t-test*. The cumulative survival rate was calculated using Kaplan-Meier survival analysis and compared between groups using the log-rank test. Only cases of cancer-related deaths were included in the analysis of cumulative survival. These analyses were performed using SPSS Statistics version 24 (IBM Corp., Armonk, NY). The data were expressed as mean ± standard deviation. Two-sided P values were considered statistically significant when less than 0.05.

2.6. Ethical statement

The study protocol was reviewed and approved by the Ethics Committee of Keio University School of Medicine (no. 20150100).

Table 1
Clinical characteristics of sporadic neoplasia and colitis-associated dysplasia/cancer in patients with ulcerative colitis.

		CAC group (n = 74)	SN group (n = 46)	P-value
Gender	Female	25 (33.8%)	11 (23.9%)	0.251
	Male	49 (66.2%)	35 (76.1%)	
Age at UC onset	(years, mean ± SD)	30.6 ± 12.6	41.3 ± 16.9	<0.001
Age at tumor detection	(years, mean ± SD)	46.2 ± 13.8	58.3 ± 12.8	<0.001
Disease duration	(years, mean ± SD)	15.7 ± 9.07	17.0 ± 12.9	0.507
Clinical activity	No activity	33 (44.6%)	42 (91.3%)	<0.001
	Active	41 (55.4%)	4 (8.7%)	
Clinical type	Relapse and remission	38 (51.3%)	41 (89.1%)	<0.001
	Chronic persistent	35 (47.3%)	3 (6.5%)	
	First attack	1 (1.4%)	2 (4.3%)	
Extent of disease	Total colitis	51 (68.9%)	32 (69.6%)	0.650
	Left-side colitis	22 (29.7%)	10 (21.7%)	
	Others	1 (1.4%)	2 (4.3%)	

Categorical variables were compared by the Chi-squared test or Fisher's exact test and continuous variables were compared by Student's *t-test*.
CAC, colitis-associated cancer; SN, sporadic neoplasia; UC, ulcerative colitis; SD, standard deviation.

3. Results

3.1. Patients' clinical characteristics

Of 266 patients who had 348 colonic lesions, 47 with 82 lesions outside the inflamed mucosa and 62 with 70 non-dysplastic lesions were excluded from this study. A total of 12 patients with 14 unclassified lesions were excluded. Among these 14 lesions, 5 and 1 were diagnosed as low grade dysplasia and tubulovillous adenoma at the first detection, respectively. However, these 6 lesions disappeared during the follow-up period. The other 7 lesions were initially suspected to be colitis-associated dysplasia at the first time. However, positivity for p53 was weak and the lesions subsequently disappeared, and the lesions were considered as inflammatory changes similar to dysplasia. The final excluded lesion was diagnosed as anal canal carcinoma. Furthermore, 25 patients with 26 sporadic adenomas that were diagnosed only by biopsied specimens were excluded. Finally, 120 patients were included in this analysis, divided into 74 patients with 97 CAC/dysplastic lesions (CAC group) and 46 patients with 58 SN lesions (SN group) (Supplemental Figure). CAC was found in 2 patients during the follow-up period after endoscopic resection of SN. To avoid confusion, these 2 patients were excluded when analyzing the prognosis.

The clinical characteristics of the CAC and SN groups are shown in Table 1. The mean age at UC onset in the CAC and SN groups was 30.6 and 41.3 years, respectively. The mean age at tumor detection in the CAC group was significantly younger compared to the SN group (46.2 vs. 58.3 years; $P < 0.001$). The CAC group had a higher percentage of chronic persistent UC compared to the SN group (47.3% vs. 6.5%; $P < 0.001$). The proportion of patients with total colitis was comparable between both groups. Less than half of patients (33/74, 44.6%) with CAC were in clinical remission, whereas 89.1% (41/46) maintained clinical remission in the SN group ($P < 0.001$).

3.2. Morphologic and endoscopic findings in the CAC and SN groups

The typical endoscopic and histological findings of colitis-associated dysplasia (Fig. 1a–d) and sporadic adenoma (Fig. 1e–h) are shown. Polypoid lesions could be found using conventional WLI (Fig. 1a); however, granular flat lesions and distinct borders, which were not recognized using WLI, could be identified using chromoendoscopy (Fig. 1b). Histological findings revealed the presence of dysplasia (Fig. 1c), with over-expression and basal positivity of p53 (Fig. 1d) in the surrounding lesions. In contrast to the colitis-associated lesions, sporadic sessile lesions with a distinct border could be easily recognized using only WLI (Fig. 1e–f). Histological findings revealed expression of p53 only in the polypoid lesions and its absence in the surrounding lesions (Fig. 1g–h).

Clinical characteristics of the lesions in the CAC and SN groups were shown in Table 2. The mean tumor size and the proportion of lesions at the proctosigmoid colon (rectum or sigmoid colon) were significantly different between the both groups. Endoscopic inflammatory severity during detection was worse in the CAC group than in the SN group, with mean Mayo endoscopic scores of 1.38 and 0.46, respectively.

We next assessed the macroscopic characteristics of intraepithelial and submucosal lesions (Table 3). The proportion of patients with intraepithelial or submucosal lesions in the SN group (91.4%) was higher than that in the CAC group (68.0%). The mean size was significantly larger in the CAC group than in the SN group (24.0 mm vs. 15.2 mm; $P < 0.005$). Most lesions in the SN group were sessile or superficial elevated. Similar to the findings of our previous report [11], superficial elevated or flat lesions were frequently observed in the CAC group. In contrast, no flat lesions were observed in the SN group. Furthermore, the proportion of lesion with depression/ulceration (likely depressed type according to the SCENIC consensus statement) was higher in the CAC group than in the SN group (7.6% vs. 3.8%). Even in patients with intraepithelial or submucosal lesions, the proportion of lesions in the proctosigmoid colon was significantly higher in the CAC group than in the SN group. Furthermore, all lesions in the SN group were distinguished from the surrounding mucosa, but only approximately one third the lesions (37.9%) in the CAC group could be distinguished from the surrounding mucosa by conventional colonoscopy. All lesions that could not be easily detected by conventional white light imaging were subsequently recognized using chromoendoscopy and/or magnifying endoscopy.

3.3. Pathological findings in the CAC and SN groups

The pathological findings of CAC and SN are shown in Table 2. The number of lesions with poor prognostic pathological findings was 21 (21.6%) in the CAC group and 2 (3.5%) in the SN group ($P = 0.002$). Interestingly, 6 lesions in the CAC group had poor prognostic pathological findings despite being non-advanced CACs.

3.4. Treatment and prognosis in the CAC and SN groups

A total of 44 patients with 55 sporadic lesions underwent local excision (endoscopic or surgical resection) within the previously inflamed mucosa (Fig. 2A). EMR (34 lesions in 25 patients) and ESD (14 lesions in 12 patients) were performed, and all lesions were completely resected. Partial colectomy was performed in 6 patients, as is standard for colorectal cancer. Another patient underwent a

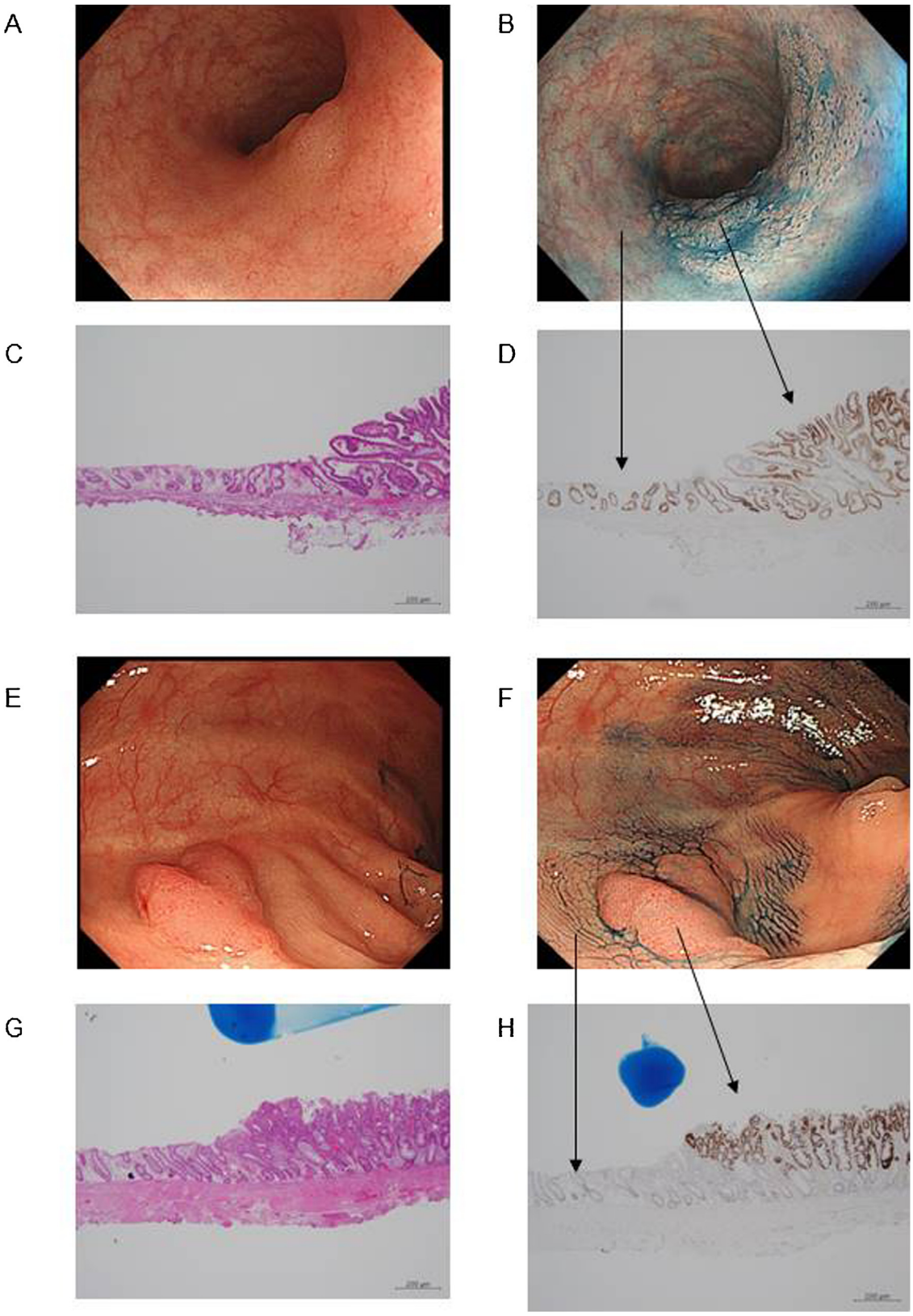

Fig. 1. Typical endoscopic and pathological findings of colitis-associated dysplasia (high grade dysplasia) (A–D) and sporadic adenoma (E–H). Endoscopic findings using conventional white light imaging. (A) A flat lesion was recognized in the surrounding area after indigo carmine dye was sprayed (B). Hematoxylin and eosin histological staining revealed the presence of dysplasia (C) The over-expression of p53 as well as its presence in the surrounding flat area was observed (arrow) (D). A solitary sessile polyp was found in the sigmoid colon. There were no flat lesions in the surrounding area of (E–F). Hematoxylin and eosin histological staining revealed the presence of tubular adenoma (G). Although p53 expression was expressed in the polyp (arrow), it was not in the surrounding area (H).

Table 2
Characteristics of macroscopic and pathological findings.

		CAC group (n = 74 patients, 97 lesions)	SN group (n = 46 patients, 58 lesions)	P-value
Location of tumor	Proctosigmoid colon	82 (84.5%)	32 (55.2%)	<0.001
	Others	15 (15.5%)	26 (44.8%)	
Mayo endoscopic score	(mean ± SD)	1.38 ± 0.86	0.46 ± 0.75	<0.001
Tumor size	(mm, mean ± SD)	32.0 ± 22.4	16.3 ± 12.6	<0.001
Depth of tumor invasion	M	51 (52.6%)	52 (89.7%)	<0.001
	SM	15 (15.5%)	1 (1.7%)	
	MP	8 (8.2%)	1 (1.7%)	
	SS	23 (23.7%)	4 (6.9%)	
por / sig / muc	(−)	76 (78.4%)	56 (96.6%)	0.003
	(+)	21 (21.6%)	2 (3.4%)	
	por	5	0	
	sig	1	0	
	mixed	12	2	

CAC, colitis-associated cancer; SN, sporadic neoplasia; SD, standard deviation; M, mucosa; SM, submucosa; MP, muscularis propria; SS, subserosa; por, poorly differentiated adenocarcinoma; sig, signet-ring cell carcinoma; muc, mucinous carcinoma; mixed, "mixed" was defined as a lesion with adenocarcinoma in addition to por / sig / muc.

Table 3
Characteristics of the endoscopic findings of intraepithelial and submucosal lesions in the colitis-associated cancer and sporadic neoplasia groups.

		CAC group (n = 66 lesions)	SN group (n = 53 lesions)	P-value
Location of tumor	Proctosigmoid colon	53 (80.3%)	27 (50.9%)	0.010
	Others	13 (19.7%)	26 (49.1%)	
Tumor size	(mm, mean ± SD)	23.1 ± 17.2	15.2 ± 12.3	0.005
SCENIC classification	Pedunculated	0 (0%)	5 (9.4%)	
	Sessile	17 (25.8%)	23 (43.4%)	
	Superficial elevated	27 (40.9%)	23 (43.4%)	<0.001
	Flat	17 (25.8%)	0 (0%)	
	Depressed	5 (7.6%)	2 (3.8%)	
	Ulcerated	2 (3.0%)	0 (0%)	0.502
	Distinct border	25 (37.9%)	53 (100%)	<0.001

CAC, colitis-associated cancer; SN, sporadic neoplasia; SD, standard deviation.

total colectomy because the lesion could not be distinguished as CAC or SN and the patient wanted to undergo total colectomy. Among patients in the SN group who received endoscopic resections, 4 new lesions (3 SNs and 1 LGD) were subsequently detected after endoscopic resections for SN during a median follow-up of 1.7 years. Three patients with SN required EMR/ESD, 1 patient with LGD required ESD.

In the CAC group, 52, 8, and 6 patients underwent total colectomy, partial colectomy, and endoscopic resection, respectively (Fig. 2B). At our institution, total colectomy is generally performed for patients with CAC. However, partial colectomy was performed in 8 patients according to their request or in consideration of their older age. Among these 8 patients, an HGD was detected during the follow-up period after partial colectomy, and the patient agreed to undergo a total colectomy (Fig. 2B). Six patients did not undergo resection because of their disseminated advanced cancers. Among these 6 patients, 5 were dead and 1 was receiving best supportive care at the end of the study period. The distinct borders of endoscopically resected lesions (5 by ESD, 1 by EMR) could be recognized using magnifying colonoscopy.

In total, only 1 patient in the SN group died during a median follow-up period of 3.2 years (IQR 1.4–4.6). Conversely, a total of 16 patients in the CAC group died during a median follow-up period of 6.1 years (IQR 1.8-11.1). Twelve patients died from cancer and 4 from other causes (fulminant hepatitis, primary sclerosing cholangitis, pulmonary infection, and gastric cancer, respectively). Mortality from colorectal cancer was significantly higher (P = 0.015) in the CAC group (12/68; 17.6%) than in the SN group (1/44; 2.3%). The 5-year cumulative survival rate for non-advanced cancer was 100% and 97.1% in the SN and CAC groups, respectively (Fig. 3A). The expected survival duration for non-advanced cancer was comparable between CAC group and SN group (P = 0.542).

Next, we assessed the prognosis after each treatment in the SN and CAC groups. In the SN group, median follow-up period in patients underwent total colectomy, partial colectomy, ESD, and EMR was 2.1, 4.6, 1.4, and 3.2 years, respectively. In the CAC group, median follow-up period in patients underwent total colectomy, partial colectomy, ESD, and EMR was 7.5, 6.8, 1.2, and 5.0 years, respectively. One patient who received partial colectomy because of old age died due to CAC recurrence. The other 3 patients (partialcolectomy, 2, endoscopicresection,1) died due to gastric cancer, fulminant hepatitis, and primary sclerosing cholangitis, respectively. None of the 5 patients in the CAC group who underwent ESD experienced recurrences or died. The 5-year cumulative survival rate was 93.8% in the SN group, and 91.9%, 80.0%, and 16.7% in CAC group patients who needed total colectomy, partial colectomy, and those who did not receive any resection, respectively (Fig. 3B). The expected survival was comparable between patients in the SN group and CAC group patients that underwent total colectomy (P = 0.263) or partial colectomy (P = 0.173).

4. Discussion

The clinical and macroscopic characteristics of CAC have been investigated in-depth. The differences in the characteristics and prognoses between CAC in UC patients and sporadic colorectal cancer in non-UC patients have also been assessed in numerous previous studies. However, to date, there have been only a few studies on the features of sporadic adenoma/cancer at previously or currently/inflamed mucosa in UC patients. Recent European

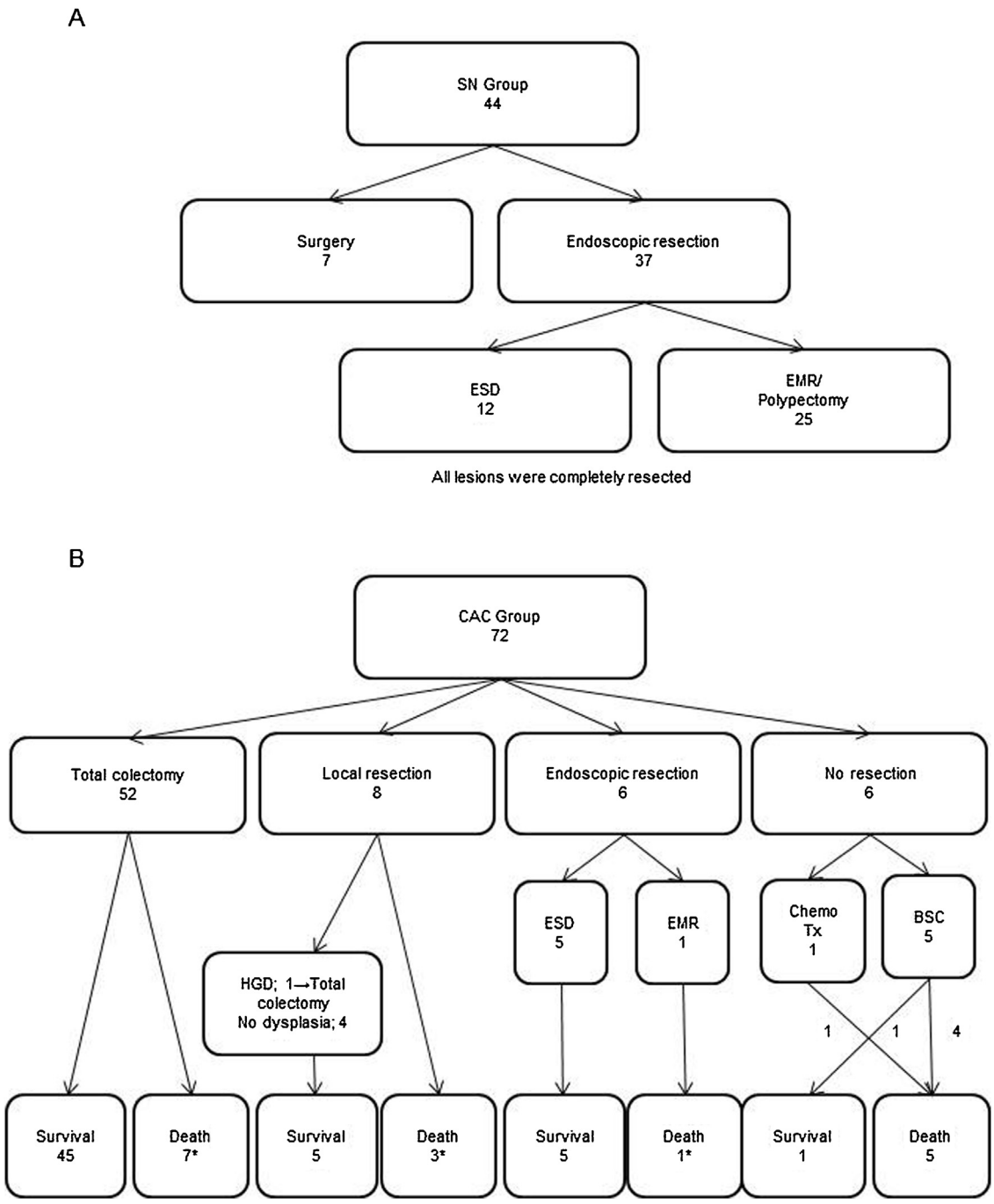

Fig. 2. Treatment options and prognosis in patients with sporadic neoplasia and colitis-associated cancer. (A) Among the 44 patients in the SN group, endoscopic resections were performed in all 44 for 52 lesions. Partial colectomy was performed in 6 patients and total colectomy in 1. Only 1 patient with advanced sporadic cancer died within the follow up period. (B) Among 72 patients in the CAC group, total colectomy, partial colectomy, and endoscopic resection was performed in 52, 8, and 6 patients, respectively. The remaining 6 patients did not undergo surgical/endoscopic resection. * A total of 4 patients in the CAC group died due to non-cancer-related reasons. CAC, colitis-associated cancer; SN, sporadic neoplasia; HGD, high-grade dysplasia; ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection; Chemo Tx, chemotherapy; BSC, best supportive care.

Crohn's and Colitis Organization consensus statements on the histopathology of IBD underlined that the distinction between CAC and SN is critical because the management of sporadic adenomas differs from that of colitis-associated dysplasia [17]. Here, we have shown that younger age at UC onset, chronic inflammation surrounding the tumor, advanced cancer, flat lesions, and histological findings with a poor prognosis (mucinous/poorly differentiated adenocarcinoma, or signet-ring cell carcinoma) are more frequently observed in patients with CAC. In terms of prognosis, we also showed that colorectal cancer-related mortality was 17.6% and 2.3% in the CAC and SN groups, respectively. Importantly, the mortality in patients with CAC was significantly lower when the CAC/dysplasia was intraepithelial dysplasia or submucosal carcinoma. To our knowledge, our study is the first to directly compare the clinical characteristics and prognosis of patients with CAC to those of patients with SN that were found only in the inflamed mucosa.

In previous studies, polypoid lesions within the most proximal extent of colitis were defined as adenoma-like dysplasia associated lesion or mass (DALM) [18]. The term "sporadic neoplasia,"

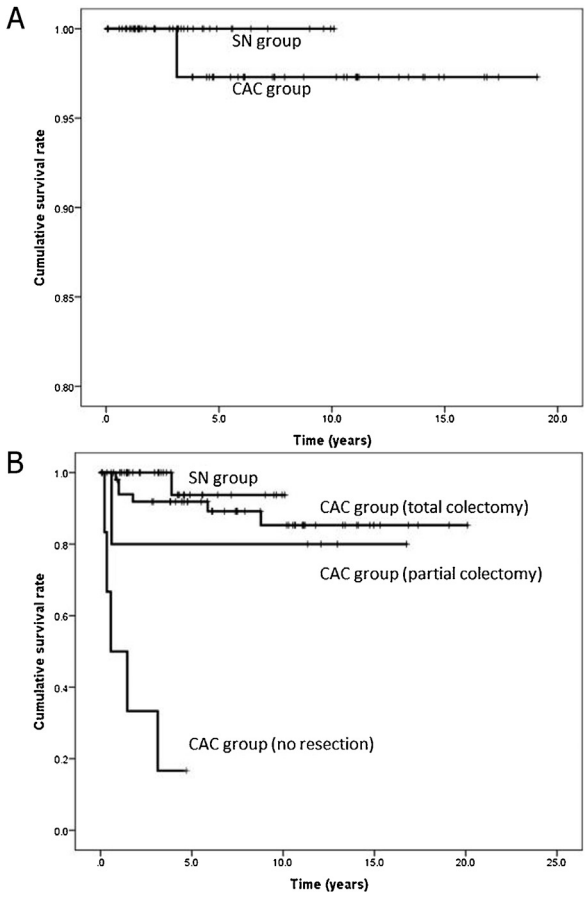

Fig. 3. (A) Cumulative survival rates for non-advanced cancer in patients in the SN and CAC groups. (B) Cumulative survival rates in patients with the SN and CAC groups (total colectomy, partial colectomy, no resection). CAC, colitis-associated cancer; SN, sporadic neoplasia.

which we used in this study for the lesions that were found in the previously or currently inflamed mucosa, may partially overlap with adenoma-like DALM. In the SCENIC consensus statement, the term "DALM" was abandoned, and classification according to morphologic features based on careful endoscopic observation is recommended [12]. However, in this situation, colitis-associated polypoid lesions in patients with chronic inflammation and sporadic polypoid lesions in patients who have maintained remission for a long time are classified into the same "polypoid" category. Under such circumstances, the results may not reflect the real clinical characteristics of UC, even in robust, well-designed clinical studies. Therefore, the differences in the clinical and endoscopic characteristics of CAC and SN have been investigated in this study.

It may be difficult to distinguish CAC/dysplasia from sporadic cancer/adenoma in some cases. To avoid misclassification based on insufficient histological evaluation of the biopsied specimens, we included only endoscopically or surgically resected lesions, enabling accurate pathological distinction in our study. Thereafter, the clinical characteristics and prognosis of "pathologically defined" CAC and SN were analyzed. We have classified CAC and SN using immunohistochemistry with p53 and Ki67 in addition to conventional pathological diagnosis. Previous studies found that p53 over-expression is frequently detected in UC dysplasia and carcinomas by immunohistochemistry [19–21]. Furthermore, the lesions of UC-associated dysplasia arise from a larger field of colorectal mucosa with a mutational burden that confers an increased risk of promoting neoplastic progression, known as field cancerization [22,23]. It is essential to perform biopsies of flat areas surrounding such lesions to assess for dysplasia [12]. After complete removal of endoscopically resectable dysplastic lesions, it is of increasing importance to endoscopically distinguish lesions from the surrounding mucosa to avoid ectopic recurrence. On the other hand, false positive p53 expression results are observed because a small proportion of non-dysplastic lesions may also be positive in UC patients. To improve the diagnostic accuracy of immunohistochemical analysis, including Ki67 expression in addition to p53 is useful to distinguish CAC from SN. In fact, Wong et al. showed that restriction of Ki67 staining to the basal third of the crypt appears to exclude a diagnosis of UC-associated dysplasia, whereas intense p53 staining suggests dysplasia [24].

Recent studies have demonstrated that the carcinogenesis of CAC and SN proceeds differently. In SN, early activation of the Wnt/β-catenin pathway, including mutations in *APC* tumor suppressor genes, is involved in the progression to malignancy, whereas *TP53* and *KRAS* mutations are early contributors to carcinogenesis in patients with CAC [25]. Recent data also indicated that the intestinal microbiome and its interaction with a functionally impaired mucosal barrier may also play a role in CAC development [26]. CACs frequently show aggressive growth and early metastases. Therefore, it is critical to detect CAC in the early stage, such as non-invasive dysplasia, because the prognosis is better in patients with intraepithelial lesions than in those with invasive CAC.

We believe that understanding the endoscopic features of dysplastic lesions, which are usually surrounded by flat areas, is critical to detect CAC in the early stage. In addition to careful observation with high definition colonoscopy, chromoendoscopy can help detect superficial elevated and flat lesions in UC patients. It is also useful for recognizing distinct lesion borders using magnifying colonoscopy [11]. Assessing borders is essential when endoscopic resection is planned.

Previously, total colectomies were performed even for patients with SN in previously inflamed mucosa because these lesions were considered to be "colitis-associated". More recent studies suggested that endoscopic polypectomy may be adequate for adenoma-like dysplastic lesions in chronic UC; however, the sample sizes were small [27–29]. Yet, there have been few studies comparing the clinical, endoscopic and pathological characteristics of CAC and SN within the inflamed mucosa of UC patients. The results from our study indicated that clinical characteristic and macroscopic findings were different between the both groups and the prognosis in the SN group is excellent even with most patients not undergoing total colectomy. Physicians and surgeons who see UC patients should recognize the endoscopic and histological differences between CAC and SN since each require different treatment; endoscopic resection or partial colectomy can be selected for SN whereas total colectomy is generally performed for CAC. In our cohort, partial colectomies or endoscopic resections were performed in patients with CAC. Most patients who did not undergo total colectomy were elderly or had other complications. A total of 5 patients received ESD because they refused total colectomy and because the endoscopists could also confirm that the CAC lesions were detectable and clearly demarcated. It should be emphasized that "diagnostic ESD" should not be performed if the lesion demarcation line is not clear in patients with CAC.

At present, total colectomy is generally recommended for patients with CAC because ectopic or metachronous recurrence of CAC should be concerned. However, the recent SCENIC consensus indicated that endoscopic resection may be allowed if the margins of the lesions are clearly recognizable. Based on this strategy, we have recently performed endoscopic resection, including ESD, in UC patients with colonic neoplasia regardless of whether it is CAC or sporadic adenoma. On the other hand, partial colectomy for advanced adenocarcinoma may be allowed in elderly patients or those with underlying disease. Because the

follow-up periods of current studies on endoscopic resection are not sufficiently long, future studies to confirm the outcome of patients with colitis-associated dysplasia who undergo ESD are required.

There are some limitations to this study. First, our study was retrospectively conducted. Second, patients with LGD were excluded from this study because some LGD spontaneously disappeared. Some lesions were first detected as LGD before progressing to HGD. We included these patients who were finally diagnosed as HGD into the CAC group. Third, the diagnosis of CAC or SN was only performed by histological findings using p53 and Ki67. Although we did not use quantitative thresholds for p53 and Ki67, the pattern of p53 or Ki67 positivity and the location of the generative or proliferative cell zone were also assessed for the diagnosis of CAC. We understand that some lesions in UC patients may be difficult to identify as CAC and SN. Therefore, we excluded these patients as unclassified cases. In the clinical setting, the consultation of a pathologist with significant experience with CAC is necessary if the diagnosis is difficult.

In conclusion, younger age at UC onset, chronic inflammation surrounding the tumor, flat lesions, and histological findings with mucinous/poorly differentiated adenocarcinoma or signet-ring cell carcinoma were more frequently observed in patients with CAC. Colorectal cancer-related mortality was low in both groups of patients with non-advanced cancer. Recognition of differences in the characteristics of CAC and SN is critical to avoid unnecessary total colectomy. Endoscopic resection can be performed in patients with SN, with a good long-term prognosis.

Conflict of interest

None declared.

Acknowledgement

We would like to thank Editage (www.editage.jp) for English language editing.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dld.2019.05.003.

References

[1] Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 2001;48:526–35.
[2] Jess T, Rungoe C, Peyrin-Biroulet L. Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. Clin Gastroenterol Hepatol 2012;10:639–45.
[3] Annesse V, Beaugerie L, Egan L, Biancone L, Bolling C, Brandts C, et al. European evidence-based consensus: inflammatory bowel disease and malignancies. J Crohns Colitis 2015;9:945–65.
[4] Claessen MM, Lutgens MW, van Buuren HR, Oldenburg B, Stokkers PC, van der Woude CJ, et al. More right-sided IBD-associated colorectal cancer in patients with primary sclerosing cholangitis. Inflamm Bowel Dis 2009;15:1331–6.
[5] Bergeron V, Vienne A, Sokol H, Seksik P, Nion-Larmurier I, Ruskone-Fourmestraux A, et al. Risk factors for neoplasia in inflammatory bowel disease patients with pancolitis. Am J Gastroenterol 2010;105:2405–11.
[6] Rubin DT, Huo D, Kinnucan JA, Sedrak MS, McCullom NE, Bunnag AP, et al. Inflammation is an independent risk factor for colonic neoplasia in patients with ulcerative colitis: a case-control study. Clin Gastroenterol Hepatol 2013;11:1601–8.
[7] Feakins RM. Inflammatory bowel disease biopsies: updated British Society of Gastroenterology reporting guidelines. J Clin Pathol 2013;66:1005–26.
[8] Choi CH, Rutter MD, Askari A, Lee GH, Warusavitarne J, Moorghen M, et al. Forty-year analysis of colonoscopic surveillance program for neoplasia in ulcerative colitis: an updated overview. Am J Gastroenterol 2015;110:1022–34.
[9] Vieth M, Behrens H, Stolte M. Sporadic adenoma in ulcerative colitis: endoscopic resection is an adequate treatment. Gut 2006;55:1151–5.
[10] Kisiel JB, Loftus Jr EV, Harmsen WS, Zinsmeister AR, Sandborn WJ. Outcome of sporadic adenomas and adenoma-like dysplasia in patients with ulcerative colitis undergoing polypectomy. Inflamm Bowel Dis 2012;18:226–35.
[11] Sugimoto S, Naganuma M, Iwao Y, Matsuoka K, Shimoda M, Mikami S, et al. Endoscopic morphologic features of ulcerative colitis-associated dysplasia classified according to the SCENIC consensus statement. Gastrointest Endosc 2017;85:639–46.
[12] Laine L, Kaltenbach T, Barkun A, McQuaid KR, Subramanian V, Soetikno R, et al. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. Gastrointest Endosc 2015;81:489–501.
[13] Kobayashi S, Fujimori T, Mitomi H, Tomita S, Ichikawa K, Imura J, et al. Immunohistochemical assessment of a unique basal pattern of p53 expression in ulcerative-colitis-associated neoplasia using computer-assisted cytometry. Diagn Pathol 2014;9:99.
[14] Fogt F, Poremba C, Shibao K, Itoh H, Kohno K, Zimmerman RL, et al. Expression of survivin, YB-1, and KI-67 in sporadic adenomas and dysplasia-associated lesions or masses in ulcerative colitis. Appl Immunohistochem Mol Morphol 2001;9:143–9.
[15] Matkowskyj KA, Chen ZE, Rao MS, Yang GY. Dysplastic lesions in inflammatory bowel disease: molecular pathogenesis to morphology. Arch Pathol Lab Med 2013;137:338–50.
[16] Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987;317:1625–9.
[17] Magro F, Langner C, Driessen A, Ensari A, Geboes K, Mantzaris GJ, et al. European consensus on the histopathology of inflammatory bowel disease. J Crohns Colitis 2013;7:827–51.
[18] Blackstone MO, Riddell RH, Rogers BH, Levin B. Dysplasia-associated lesion or mass (DALM) detected by colonoscopy in long-standing ulcerative colitis: an indication for colectomy. Gastroenterology 1981;80:366–74.
[19] Chaubert P, Benhattar J, Saraga E, Costa J. K-ras mutations and p53 alterations in neoplastic and nonneoplastic lesions associated with longstanding ulcerative colitis. Am J Pathol 1994;144:767–75.
[20] Harpaz N, Peck AL, Yin J, Fiel I, Hontanosas M, Tong TR, et al. p53 protein expression in ulcerative colitis-associated colorectal dysplasia and carcinoma. Hum Pathol 1994;25:1069–74.
[21] Fogt F, Zhuang Z, Poremba C, Dockhorn-Dworniczak B, Vortmeyer A. Comparison of p53 immunoexpression with allelic loss of p53 in ulcerative colitis-associated dysplasia and carcinoma. Oncol Rep 1998;5:477–80.
[22] Hussain SP, Amstad P, Raja K, Ambs S, Nagashima M, Bennett WP, et al. Increased p53 mutation load in noncancerous colon tissue from ulcerative colitis: a cancer-prone chronic inflammatory disease. Cancer Res 2000;60:3333–7.
[23] Leedham SJ, Graham TA, Oukrif D, McDonald SA, Rodriguez-Justo M, Harrison RF, et al. Clonality, founder mutations, and field cancerization in human ulcerative colitis-associated neoplasia. Gastroenterology 2009;136:542–50.
[24] Wong NA, Mayer NJ, MacKell S, Gilmour HM, Harrison DJ. Immunohistochemical assessment of Ki67 and p53 expression assists the diagnosis and grading of ulcerative colitis-related dysplasia. Histopathology 2000;37:108–14.
[25] Robles AI, Traverso G, Zhang M, Roberts NJ, Khan MA, Joseph C, et al. Whole-Exome Sequencing Analyses of Inflammatory Bowel Disease-Associated Colorectal Cancers. Gastroenterology 2016;150:931–43.
[26] Richard ML, Liguori G, Lamas B, Brandi G, da Costa G, Hoffmann TW, et al. Mucosa-associated microbiota dysbiosis in colitis associated cancer. Gut Microbes 2018;9:131–42.
[27] Engelsgjerd M, Farraye FA, Odze RD. Polypectomy may be adequate treatment for adenoma-like dysplastic lesions in chronic ulcerative colitis. Gastroenterology 1999;117:1288–94.
[28] Rubin PH, Friedman S, Harpaz N, Goldstein E, Weiser J, Schiller J, et al. Colonoscopic polypectomy in chronic colitis: conservative management after endoscopic resection of dysplastic polyps. Gastroenterology 1999;117:1295–300.
[29] Odze RD, Farraye FA, Hecht JL, Hornick JL. Long-term follow-up after polypectomy treatment for adenoma-like dysplastic lesions in ulcerative colitis. Clin Gastroenterol Hepatol 2004;2:534–41.