

Digestion

Manuscript:	DIG-2023-10-5/R1 RESUBMISSION
Title:	Characteristics and prognosis of sporadic neoplasias detected in patients with ulcerative colitis
Authors(s):	Noriko Yamamoto (Co-author), Ken Yamashita (Corresponding Author), Yudai Takehara (Co-author), Shin Morimoto (Co-author), Fumiaki Tanino (Co-author), Yuki Kamigaichi (Co-author), Hidenori Tanaka (Co-author), Koji Arihiro (Co-author), Fumio Shimamoto (Co-author), Shiro Oka (Co-author)
Keywords:	characteristics, metachronous lesion, prognosis, sporadic neoplasia, Ulcerative colitis, ulcerative colitis-associated neoplasia
Type:	Research Article

Research Article
***Characteristics and prognosis of sporadic neoplasias detected in
patients with ulcerative colitis***

Noriko Yamamoto^a, MD, Ken Yamashita^{a*}, MD, PhD, Yudai Takehara^a, MD, Shin Morimoto^a, MD, Fumiaki Tanino^a, MD, Yuki Kamigaichi^a, MD, Hidenori Tanaka^a, MD, PhD, Koji Arihiro^b, MD, PhD, Fumio Shimamoto^c, MD, PhD, Shiro Oka^a, MD, PhD

^a Department of Gastroenterology, Hiroshima University Hospital, Hiroshima, Japan

^b Department of Anatomical Pathology, Hiroshima University Hospital, Hiroshima, Japan

^c Faculty of Health Sciences, Hiroshima Cosmopolitan University, Hiroshima, Japan

Short Title: sporadic neoplasias in patients with ulcerative colitis

*** Corresponding author**

Department of Gastroenterology, Hiroshima University Hospital

1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

Telephone: +81 82 257 5193

Fax: +81 82 257 5194

Email: ken-yama5@hiroshima-u.ac.jp

Keywords: ulcerative colitis, sporadic neoplasia, ulcerative colitis-associated neoplasia, metachronous lesion, characteristics, prognosis

Word count: Main text, 3508 (excluding abstract); Abstract, 243

Abstract

Introduction: Patients with ulcerative colitis (UC) develop not only UC-associated neoplasias but also sporadic neoplasias (SNs). However, few studies have described the characteristics of SNs in patients with UC. Therefore, this study aimed to evaluate the clinical features and prognosis of SNs in patients with UC.

Methods: A total of 141 SNs in 59 patients with UC, detected by surveillance colonoscopy at Hiroshima University Hospital between January 1999 and December 2021, were included. SNs were diagnosed based on their location, endoscopic features, and histopathological findings along with immunohistochemical staining for Ki67 and p53.

Results: Of the SNs, 91.5% were diagnosed as adenoma and 8.5% were diagnosed as carcinoma (Tis carcinoma, 3.5%; T1 carcinoma, 5.0%). Most lesions (61.0%) were located in the right colon, 31.2% were located in the left colon, and 7.8% were located in the rectum. When classified based on site of lesion, 70.9% of SNs occurred outside and 29.1% within the affected area. Of all SNs included, 95.7% were endoscopically resected and 4.3% were surgically resected. Among the 59 patients included, synchronous SNs occurred in 23.7% and metachronous multiple SNs occurred in 40.7% during surveillance. The 5-year cumulative incidence of metachronous multiple SNs was higher in patients with synchronous multiple SNs (54.2%) than in those without synchronous multiple SNs (46.4%).

Conclusion: Patients with UC with synchronous multiple SNs are at a higher risk of developing metachronous multiple SNs and may require closer follow-up by total colonoscopy than patients without synchronous SNs.

Introduction

Recently, the prevalence of ulcerative colitis (UC) has been increasing worldwide [1, 2]. However, the need for colectomy in patients with refractory disease has been decreasing as recent advances in UC treatment have led to an increasing proportion of patients achieving remission [3-5]. Moreover, the number of surgeries for UC-associated dysplasia (UCAD)/UC-associated carcinoma (UCAC) is increasing [5]. UC-associated neoplasias (UCANs) are known to develop in patients with long-standing UC [6, 7]. Additionally, sporadic neoplasias (SNs) are also detected in patients with UC [8].

Total proctocolectomy is recommended as the standard procedure for patients with UCAC or high-grade dysplasia (HGD) [9–11], because approximately 43%–50% of them may have concomitant malignancies at the time of colectomy [12–15]. In contrast, the management of low-grade dysplasia (LGD) in patients with UC remains controversial [10, 11]. The Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations (SCENIC) statement suggests that LGDs can be resected endoscopically if they are endoscopically visible [16]. However, there is no clear consensus regarding the treatment method for endoscopically invisible dysplasia [17]. Although the reported progression rate from LGD to HGD or carcinoma varies from 0%–53% [18-21], the presence of LGD is a risk factor for higher-grade neoplasia. Proctocolectomy eliminates the risk of colorectal carcinoma (CRC) in patients with UC-associated LGD. However, the decision to perform proctocolectomy or continued surveillance in patients with flat and endoscopically invisible LGD should be individualized and discussed between the patient, gastroenterologist, and colorectal surgeon [9, 22]. In contrast, SNs have a better prognosis than UCANs [23, 24] and are good indicators for local excision by endoscopic resection (ER) or partial colectomy, even in patients with UC [8, 9, 25]. The SCENIC statement recommends ER and surveillance colonoscopy (SCS) for polypoid lesions [16]; however, it does not clearly distinguish UCANs from SNs [16]. On the other hand, the European Crohn's and Colitis Organisation (ECCO) consensus on the diagnosis and management of UC describes that polypoid dysplasia could be adequately treated by polypectomy if the lesion can be completely excised and there is no evidence of non-polypoid or invisible dysplasia elsewhere in the colon [9]. Furthermore, sporadic adenomas in patients with UC are also suggested to be treated as in patients without UC in this statement. However, sporadic adenoma is defined as a polyp occurring in an area proximal to the microscopic level of inflammation, with no dysplasia in the flat mucosa [9]. Although various studies have been conducted on UCANs, they did not strictly distinguish between UCAN and SN in patients with UC [24, 26, 27]. Therefore, this study aimed to evaluate the clinical features and prognosis of SNs in patients with UC.

Methods

Ethics statements

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the Hiroshima University Hospital (approval number: E2022-0318; registration date: May 12, 2023). All patients provided written informed consent before participation.

Patients

In total, 974 patients with UC who underwent endoscopic or surgical resection at the Hiroshima University Hospital between January 1999 and December 2021 were included. Of them, we retrospectively reviewed the medical records of 143 consecutive patients with 300 neoplasias detected using SCS. We excluded 75 patients with 99 UCANs diagnosed from resected specimens and 47 patients with 60 serrated lesions. This is because serrated lesions progress to CRCs through the serrated neoplasia pathway, which is different from the adenoma-carcinoma pathway [28, 29]. Finally, 59 patients with UC and 141 SNs were enrolled (Figure 1). No patient had concurrent UCAN at the time of initial SN detection. However, one patient developed UCANs during the follow-up period after the initial SN diagnosis. Although this patient and the SNs that occurred in this patient were included, the UCANs that occurred in this patient were excluded from this study. In this study, SNs detected within 2 months of the initial SN detection were defined as synchronous SNs, and those detected 2 months after the initial SN detection were defined as metachronous SNs [30, 31].

Endoscopic examination

In principle, we perform total colonoscopy (TCS) annually for patients with UC with left-sided or total colitis and a disease duration of > 7 years, if possible, in the remission stage. Endoscopists with at least 5 years of endoscopic and 1000 colonoscopies experience performed SCS for patients with UC. We also perform step and target biopsies. Step biopsy is performed by collecting a sample from each segment: the terminal ileum, ascending colon, transverse colon, descending colon, sigmoid colon, Ra (upper rectum), and Rb (lower rectum). Target biopsy is performed for lesions with features that indicate UCAN, such as slight elevation/depression of the mucosa, focal friability, obscure vascular pattern, discoloration (slight redness or paleness), villous mucosa (velvety appearance), or irregular nodularity [32, 33]. In addition, when a lesion (UCAN or SN) is detected, we perform a biopsy from

the mucosa near the lesion. In this study, we used the term "within the affected mucosa" when the histopathological findings of the biopsy from the mucosa near the lesion showed active inflammation or post-inflammatory changes (crypt architectural distortion or atrophy) [34], and "outside the affected mucosa" in other cases. All colorectal lesions were investigated using white light and narrowband imaging and/or chromo-magnification (indigo carmine). Additional magnifying observations with crystal violet were performed for colorectal lesions with irregular pit patterns. According to the Kudo-Tsuruta classification, lesions are categorized as having type I, II, IIIL, IIIS, IV, VI, or VN pit patterns [35].

Indication for treatment

Neoplasias within the UC-affected area can be UCANs or SNs. In contrast, neoplasias outside the UC-affected area are definite SNs. However, the UC-affected area sometimes extends more proximally, making it difficult to detect neoplasias within the UC-affected area. Therefore, we resected all neoplasias in patients with UC unless the patient was in poor general condition or refused to undergo neoplasia resection. The lesions outside the affected area were treated as SNs in non-UC patients: ER for lesions suspected of adenomas, mucosal carcinomas, or superficial submucosal invasive carcinomas and partial colectomy for lesions suspected of carcinomas invading the deep submucosal layer or deeper. For lesions within the affected area, ER was performed if the lesion was endoscopically well-defined, and no dysplasia was detected using biopsy from four points on the surrounding mucosa. The lesions with endoscopically indistinct borders or with dysplasias in the surrounding mucosa were considered UCANs and excluded from this study. The final diagnosis of UCAN or SN was based on the findings of resected specimens. Total colectomy was performed for UCANs diagnosed as carcinoma or HGD on biopsy of the pre-treatment lesion. For UCANs diagnosed as LGD on biopsy from a pretreatment lesion with an endoscopically indistinct border, the decision to perform total colectomy or close follow-up was discussed among several experienced physicians and gastrointestinal pathologists.

Histopathological assessment

All resected specimens were fixed in 10% formalin, sliced into 2-mm sections, embedded in paraffin, serially sectioned, stained with hematoxylin and eosin, and examined microscopically. The histopathological diagnosis of SNs was made according to the World Health Organization classification system [36]. The depth of submucosal invasion was determined on the basis of the

Japanese Society for the Colon and Rectum Classification [31]. Accordingly, lesions were classified as adenomas (including tubular adenoma, tubulovillous adenoma, and villous adenoma), Tis carcinoma (intramucosal carcinoma), T1a carcinoma (superficially submucosal invasive carcinoma: submucosal invasive depth < 1000 μ m), or T1b carcinoma (deeply submucosal invasive carcinoma: submucosal invasive depth \geq 1000 μ m) [31]. In all cases, the histopathological diagnosis of the resected lesions was confirmed and reviewed by more than one gastrointestinal pathologist.

Immunohistochemical evaluation of Ki67 and p53 expressions was performed to distinguish between UCANs and SNs. In UCANs, Ki67-positive cells are mainly found at the basal side of the mucosa, and tumor cells differentiate towards the superficial side of the mucosa, which is the “bottom-up morphology.” Conversely, in SNs, particularly in conventional tubular adenomas, Ki67-positive cells are mainly found at the superficial zone of the mucosal layer, and tumor cells differentiate towards the basal side of the mucosa, which is the “top-down morphology.” Additionally, UCANs show a significantly higher degree of p53 expression than sporadic adenomas [37], which is also useful to differentiate between UCANs and SNs. In cases where it was difficult to differentiate between SNs and UCANs, the final diagnosis was established by at least two expert pathologists (KA and FS).

Investigated variables

The patients’ clinicopathological characteristics (age, sex, UC duration, type of UC, clinical course, and presence or absence of synchronous multiple lesions) and clinicopathological features of the SNs (tumor location, background mucosa, tumor size, color, gross type, pit pattern [38], histology, and treatment method) were evaluated. Additionally, the development of metachronous multiple SNs after the first SN detection as the long-term prognosis according to the number, histology, size, and background mucosa of the initial lesions was evaluated.

Statistical analysis

Data are expressed as mean \pm standard deviation, median with range, or percentages. The incidence rate of metachronous lesions after the initial SNs was calculated using the Kaplan–Meier method. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using JMP software, version 16 (SAS Institute, Cary, NC, USA).

Results

The clinical features of the enrolled patients are presented in Table 1. The mean age at the first SN detection was 58.8 years, and the median duration of UC was 7 years. Males comprised 64.4% of the enrolled patients. The most common UC type was total colitis (47.5%). Regarding their clinical course, 49.2% of patients presented with the relapse-remitting type, 23.7% with the chronic continuous type, and 27.1% with the first attack type. Of the 59 patients, 23.7% had multiple SNs during the first detection. Metachronous multiple SNs occurred in 40.7% of the patients. Furthermore, 14 patients had synchronous SNs at initial SN detection, and 24 developed metachronous SNs during the follow-up period after initial SN detection.

The clinicopathological features of the enrolled lesions are presented in Table 2. SNs occurred in 61.0% of patients in the right colon, 31.2% in the left colon, and 7.8% in the rectum. When classified as outside or within the affected area of UC, 70.9% of SNs occurred outside and 29.1% within the affected area. Metachronous SNs tended to occur outside the affected area if the initial lesions were located outside the affected area. Whereas if the initial lesions were located within the affected area, metachronous SNs tended to occur both outside and inside the affected area (Figure 2). The mean tumor size was 5.8 mm. The color was reddish in 21.3% of the lesions and normal in 78.7%. The gross tumor type was protruded in 73.1% of the lesions and superficial in 26.9%. Additionally, we assessed the pit patterns of the lesions. Overall, 86.5% of the lesions were classified as type IIIIL, 10.7% as type VI (5 adenomas, 4 Tis carcinomas, and 6 T1 carcinomas), and only 0.7% as type VN (1 T1 carcinoma).

The frequency of adenomas among all SNs was 91.5%; that of Tis and T1 carcinoma was 3.5% and 5.0%, respectively. Among the 141 SNs, 135 (95.7%) were endoscopically resected (endoscopic mucosal resection or endoscopic submucosal dissection). Partial colectomy was performed in only six lesions (4.3%), of which five were T1b carcinomas and the remaining was an adenoma close to a T1b carcinoma.

The clinicopathological features of the carcinomas are presented in Table 3. Lesion numbers (nos.) 3 and 4 were synchronous carcinomas detected in the same patient. Of the 12 sporadic carcinomas in 11 patients, five lesions occurred within 1 year after the onset of UC. All sporadic carcinomas had adenoma components and were diagnosed as sporadic based on the expression patterns of Ki67 and p53 in the adenoma component. Most UC cases were of total colitis (7/12 cases). Half of the lesions occurred outside the affected area, and half within the affected area. Most of the lesions (10/12 cases) were reddish. All T1b carcinomas were surgically resected, whereas T1a and Tis carcinomas were endoscopically resected. Of the 11 patients, four (lesions nos. 3, 4, 7, 9, and 12) had synchronous SNs at the time of carcinoma detection. Metachronous SNs after carcinomas occurred in three patients (lesions nos. 2, 7, and 12). Only the patient with lesion no. 9 had metachronous

adenomas before the carcinoma (lesion no. 9) occurred, and the prior lesions were a 6-mm and 5-mm adenoma, both of which were resected endoscopically.

Figure 3 illustrates the Kaplan–Meier curves for the cumulative incidence rate of metachronous SNs. The histology, size, and background mucosa of the initial lesions were not associated with the incidence of metachronous lesions. The 5-year and 10-year cumulative incidence rate of metachronous multiple SNs were significantly higher in patients with synchronous multiple SNs than in those without (61% and 82% versus [vs.] 42% and 51%).

Discussion

Our data showed that SNs in patients with UC were more likely to occur outside the affected mucosa than within, and that patients with multiple SNs at the time of initial SN detection were more likely to develop multiple metachronous lesions in subsequent years. Furthermore, half of the SNs occurred within 7 years of UC onset, suggesting that SNs can occur earlier than UCANs. Therefore, the SCS method for detecting UCANs and SNs in patients with UC requires reconsideration. UCANs occur only within the affected area of UC, whereas SNs occur both outside and within the affected area [8, 39]. Moreover, the differences in the characteristics and prognoses between CAC in patients with UC and sporadic CRC in patients without UC have been assessed in several previous studies; patients with CAC and UC had younger age at carcinoma diagnosis, higher rate of synchronous multiple lesions and mucinous/signet ring cell carcinomas, and poorer prognosis [24, 26, 27]. However, limited studies have been conducted on the features and prognosis of sporadic adenoma/carcinoma, particularly within the affected area [8].

Recent ECCO histopathological statements have indicated that some pathological features help differentiate UCANs from SNs; associated flat dysplasia (no sharp delineation), irregular neoplastic glands (varying configuration, size, and diameter) with varying amounts of stroma, increased (mononuclear) lamina propria inflammation, and a mixture of benign/dysplastic crypts at the surface [40]. Furthermore, recent studies have shown that immunohistochemistry also helps differentiate UCANs from SNs. Evaluation of the proliferative zone is considered particularly useful for the differential diagnosis of UC-associated LGD and low-grade sporadic adenoma [25, 41]. Although the results of such evaluations are not always conclusive, the distribution of Ki67-positive cells in the mucosa is one of the useful findings to distinguish UCANs from SNs [25, 40, 41]. In non-neoplastic mucosa, Ki67-staining is restricted to the basal third of the crypt. However, Ki67-staining expands to the upper epithelium in dysplasias. Moreover, in some dysplasias and all invasive carcinomas, Ki67-

staining is diffusely distributed throughout the crypts [42]. In contrast, Ki67-positive cells are mainly distributed to the upper side of the epithelium in sporadic adenoma [43, 44]. Similar to UCAC, sporadic carcinoma shows diffuse contributions of Ki67-positive cells [45]. Regarding UCANs, most lesions show diffuse and strong expression of p53 and the occasional null expression of p53. However, in intramucosal lesions, such as LGD, p53 expression is not universal but is mainly distributed at the basal side of the crypts [25, 41, 46]. In contrast, most SNs show weaker p53 expression than UCANs, although some SNs show strong p53 expression, especially in high-grade lesions [37]. Some UCANs also have a surrounding flat area with p53 overexpression, which is absent in SNs that instead have a distinct border between the neoplastic glands and the surrounding mucosa [8, 25].

The terms “dysplasia-associated lesion or mass,” “adenoma-like,” and “non-adenoma-like” were abandoned in the SCENIC statement. Instead, classification according to the lesion morphology was recommended; however, this classification does not distinguish UCANs from SNs [16]. Therefore, both UC-associated and sporadic polypoid lesions within the UC-affected area in patients with UC fall into the same category. Nonetheless, it is important to distinguish between UCANs and SNs because they have different prognoses and require varied treatment strategies [40]. Hence, we evaluated only endoscopically or surgically resected lesions and divided them into UCANs and SNs based on endoscopic findings and histopathology with immunohistochemical staining. The majority of the enrolled SNs were diagnosed as adenomas (91.5%). Moreover, there were no advanced-stage carcinomas in this study, which may be because patients with UC undergo SCS more frequently than non-UC patients, essentially every year in our hospital.

Several reports have described the low prevalence of adenomatous polyps in patients [47-50]. However, one study also showed that the rate of adenomatous sporadic polyps outside the affected area in patients with UC was not different from that in patients without UC (13.1% vs. 13.4%) [47].

Regarding patients without UC, the National Polyp Study Workgroup reported that the risk of metachronous lesions differs according to the size, number, or histology of the initial lesions [51]. According to the United States guidelines published in 2012 [52], the interval for colonoscopy after screening and ER is defined based on the characteristics of the resected lesions namely, size (< 10 mm/≥ 10 mm), number (1–2/3–10/≥ 11), and histopathology (tubular adenoma/villous adenoma/sessile serrated polyp/traditional serrated adenoma) of lesions. The British guidelines in 2010 [22] also recommended a similar SCS method after ER based on the number or size of polyps detected during the initial colonoscopy. Furthermore, our institution previously reported that male sex, multiple lesions at initial colonoscopy, and carcinoma at initial colonoscopy were the relative risk

factors for the incidence of a lesion indicated for ER in the non-UC population [53]. In contrast, in this study, we found that patients with UC with multiple SNs at the time of initial SN detection had a higher rate of subsequent metachronous multiple lesions than patients with UC with only one initial lesion, similar to the characteristics of neoplasias in non-UC patients. However, patient sex, lesion histology, tumor size, and lesion site were not associated with the incidence of metachronous lesions in our study. Although approximately half of the enrolled lesions developed outside the UC-affected area and half developed within the UC-affected area, metachronous lesions after the first SNs tended to develop outside the affected area, particularly when the first lesions occurred in the unaffected area.

Recent guidelines have suggested some SCS strategies for patients with UC, such as performing SCS for patients with left-sided colitis or total colitis with a UC duration of 8–10 years or more, because they have a higher CRC risk than non-UC patients. In contrast, patients with ulcerative proctitis are not indicated for SCS because they have similar CRC risks to non-UC patients [9, 54, 55]. However, these strategies focus on reducing UCAC-associated morbidity and mortality. Approximately two-thirds of the patients with UC have left-sided colitis or proctitis [56], and most UCANs occur in the left-sided colon, particularly in the rectum and sigmoid colon [21, 24, 57]. Therefore, several studies used sigmoidoscopy as a surveillance tool for UC [49, 57]. However, patients with UC also develop SNs, not only UCANs. Additionally, as our results demonstrated, SNs occur both within and outside the UC-affected area. This suggests an insufficiency of sigmoidoscopy and the need for TCS to detect SNs in patients with UC. Furthermore, the present data suggested that SCS for patients with UC with multiple SNs should be performed according to the colorectal polyp guidelines for non-UC patients, even if they have proctitis-type UC or have UC duration for < 8 years, although several guidelines for inflammatory bowel disease recommend periodic SCS only for patients with left-sided or total colitis-type UC with UC duration > 8–10 years [9, 10, 54, 55] and not for patients with proctitis-type UC or UC duration < 8 years.

Nonetheless, this study had some limitations. First, this study included only a few carcinomas, and therefore did not adequately assess the characteristics and prognosis of carcinomas. Further data is required to evaluate the characteristics and prognosis of carcinomas. Second, because mucosal inflammation complicates recognition of tumor margins, SNs within the inflamed mucosa could have been missed, especially for small lesions, and not all SNs, including small adenomas, could have been evaluated. To avoid missing lesions within the inflammatory mucosa, it is necessary to aim for more mucosal quiescence of UC and to perform SCS during the remission phase. In addition, it is possible that some small adenomas were missed at the initial SCS and mistakenly included as

metachronous SNs. This may suggest that the cumulative incidence of metachronous SNs may be overestimated. Finally, this was a single-center retrospective study conducted in a tertiary care center; therefore, the results of this study may not be generalizable to the entire population of patients with UC.

In conclusion, attention should be paid to the occurrence of SNs as well as UCANs, even in patients with UC. Both affected and unaffected areas should be screened, regardless of the degree or extent of UC inflammation to detect SNs, along with careful surveillance using TCS, particularly in patients with UC with multiple SNs, because they tend to develop new lesions.

Statements

Statement of Ethics

Ethical approval: This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the Hiroshima University Hospital (approval number: E2022-0318; registration date: May 12, 2023).

Consent to participate: All patients were informed of the risks and benefits of colonoscopy and provided written informed consent before participation.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

Study design: Shiro Oka, Ken Yamashita, and Noriko Yamamoto. Sample collection: Noriko Yamamoto, Ken Yamashita, Yudai Takehara, Shin Morimoto, Fumiaki Tanino, Yuki Kamigaichi, and Hidenori Tanaka. Sample evaluation: Koji Arihiro and Fumio Shimamoto. Data collection: Noriko Yamamoto. Data analysis: Noriko Yamamoto. Manuscript writing: Noriko Yamamoto and Ken Yamashita. All authors have read and approved the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are not openly available due to the privacy of patients and are available from the corresponding author upon reasonable request. Data are in controlled access data storage at Hiroshima University Hospital.

References

- 1 Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet*. 2017;390(10114):2769–78.
- 2 Kaplan GG, Ng SC. Understanding and preventing the global increase of inflammatory bowel disease. *Gastroenterology*. 2017;152(2):313–321.e2.
- 3 Eriksson C, Cao Y, Rundquist S, Zhulina Y, Henriksson I, Montgomery S, et al. Changes in medical management and colectomy rates: a population-based cohort study on the epidemiology and natural history of ulcerative colitis in Örebro, Sweden, 1963–2010. *Aliment Pharmacol Ther*. 2017;46(8):748–57.
- 4 Noguchi T, Ishihara S, Uchino M, Ikeuchi H, Okabayashi K, Futami K, et al. Clinical features and oncological outcomes of intestinal cancers associated with ulcerative colitis and Crohn’s disease. *J Gastroenterol*. 2023;58(1):14–24.
- 5 Uchino M, Ikeuchi H, Hata K, Okada S, Ishihara S, Morimoto K, et al. Changes in the rate of and trends in colectomy for ulcerative colitis during the era of biologics and calcineurin inhibitors based on a Japanese nationwide cohort study. *Surg Today*. 2019;49(12):1066–73.
- 6 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(6):639–45.
- 7 Colman RJ, Rubin DT. Histological inflammation increases the risk of colorectal neoplasia in ulcerative colitis: a systematic review. *Intest Res*. 2016;14(3):202–10.
- 8 Mutaguchi M, Naganuma M, Sugimoto S, Fukuda T, Nanki K, Mizuno S, et al. Difference in the clinical characteristic and prognosis of colitis-associated cancer and sporadic neoplasia in ulcerative colitis patients. *Dig Liver Dis*. 2019;51(9):1257–64.
- 9 Magro F, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: Definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. *J Crohns Colitis*. 2017;11(6):649–70.
- 10 Matsuoka K, Kobayashi T, Ueno F, Matsui T, Hirai F, Inoue N, et al. Evidence-based clinical practice guidelines for inflammatory bowel disease. *J Gastroenterol*. 2018;53(3):305–53.

- 11 Ross H, Steele SR, Varma M, Dykes S, Cima R, Buie WD, et al. Practice parameters for the surgical treatment of ulcerative colitis. *Dis Colon Rectum*. 2014;57(1):5–22.
- 12 Bernstein CN, Shanahan F, Weinstein WM. Are we telling patients the truth about surveillance colonoscopy in ulcerative colitis? *Lancet*. 1994;343(8889):71–4.
- 13 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(2):366–74.
- 14 Riddell RH, Goldman H, Ransohoff DF, Appelman HD, Fenoglio CM, Haggitt RC, et al. Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. *Hum Pathol*. 1983;14(11):931–68.
- 15 Torres C, Antonioli D, Odze RD. Polypoid dysplasia and adenomas in inflammatory bowel disease: a clinical, pathologic, and follow-up study of 89 polyps from 59 patients. *Am J Surg Pathol*. 1998;22(3):275–84.
- 16 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(3):489–501.e26.
- 17 Shah SC, Itzkowitz SH. Colorectal cancer in inflammatory bowel disease: mechanisms and management. *Gastroenterology*. 2022;162(3):715–730.e3.
- 18 Befrits R, Ljung T, Jaramillo E, Rubio C. Low-grade dysplasia in extensive, long-standing inflammatory bowel disease: a follow-up study. *Dis Colon Rectum*. 2002;45(5):615–20.
- 19 Lim CH, Dixon MF, Vail A, Forman D, Lynch DAF, Axon ATR. Ten year follow up of ulcerative colitis patients with and without low grade dysplasia. *Gut*. 2003;52(8):1127–32.
- 20 Connell WR, Lennard-Jones JE, Williams CB, Talbot IC, Price AB, Wilkinson KH. Factors affecting the outcome of endoscopic surveillance for cancer in ulcerative colitis. *Gastroenterology*. 1994;107(4):934–44.
- 21 Ullman T, Croog V, Harpaz N, Sachar D, Itzkowitz S. Progression of flat low-grade dysplasia to advanced neoplasia in patients with ulcerative colitis. *Gastroenterology*. 2003;125(5):1311–9.
- 22 Cairns SR, Scholefield JH, Steele RJ, Dunlop MG, Thomas HJ, Evans GD, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). *Gut*. 2010;59(5):666–89.

- 23 Annese 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(11):945–65.
- 24 Watanabe T, Konishi T, Kishimoto J, Kotake K, Muto T, Sugihara K, et al. Ulcerative colitis-associated colorectal cancer shows a poorer survival than sporadic colorectal cancer: a nationwide Japanese study. *Inflam Bowel Dis*. 2011;17(3):802–8.
- 25 Vieth M, Behrens H, Stolte M. Sporadic adenoma in ulcerative colitis: endoscopic resection is an adequate treatment. *Gut*. 2006;55(8):1151–5.
- 26 Jensen AB, Larsen M, Gislum M, Skriver MV, Jepsen P, Nørgaard B, et al. Survival after colorectal cancer in patients with ulcerative colitis: a nationwide population-based Danish study. *Am J Gastroenterol*. 2006;101(6):1283–7.
- 27 Leowardi C, Schneider ML, Hinz U, Harnoss JM, Tarantino I, Lasitschka F, et al. Prognosis of ulcerative colitis-associated colorectal carcinoma compared to sporadic colorectal carcinoma: A matched pair analysis. *Ann Surg Oncol*. 2016;23(3):870–6.
- 28 Noffsinger AE. Serrated polyps and colorectal cancer: new pathway to malignancy. *Annu Rev Pathol*. 2009;4:343–64.
- 29 Kambara T, Simms LA, Whitehall VLJ, Spring KJ, Wynter CV, Walsh MD, et al. BRAF mutation is associated with DNA methylation in serrated polyps and cancers of the colorectum. *Gut*. 2004;53(8):1137–44.
- 30 National Cancer Institute, Surveillance, Epidemiology and End Results Program, Bethesda MD. The 2007 multiple primary and histology coding rules; 2007.
- 31 Japanese Society for Cancer of the Colon and Rectum. Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma: the 3-d. English ed. Secondary Publication. *J Anus Rectum Colon*; 2019;3(4):175-95.
- 32 Oka S, Tanaka S, Chayama K. Detection of nonpolypoid colorectal neoplasia using magnifying endoscopy in colonic inflammatory bowel disease. *Gastrointest Endosc Clin N Am*. 2014;24(3):405–17.
- 33 Oka S, Uraoka T, Watanabe K, Hata K, Kawasaki K, Mizuno K, et al. Endoscopic diagnosis and treatment of ulcerative colitis-associated neoplasia. *Dig Endosc*. 2019;31(Suppl 1):26–30.
- 34 Gheorghe C, Cotruta B, Iacob R, Becheanu G, Dumbrava M, Gheorghe L. Endomicroscopy for assessing mucosal healing in patients with ulcerative colitis. *J Gastrointest Liver Dis*. 2011;20(4):423–6.

- 35 Kudo S, Hirota S, Nakajima T, Hosobe S, Kusaka H, Kobayashi T, et al. Colorectal tumours and pit pattern. *J Clin Pathol*. 1994;47(10):880–5.
- 36 Boman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO classification of tumours of the digestive system. 4th ed. Lyon, France: IARC; 2010.
- 37 Walsh SV, Loda M, Torres CM, Antonioli D, Odze RD. P53 and beta catenin expression in chronic ulcerative colitis-associated polypoid dysplasia and sporadic adenomas: an immunohistochemical study. *Am J Surg Pathol*. 1999;23(8):963–9.
- 38 Kudo S, Tamura S, Nakajima T, Yamano H, Kusaka H, Watanabe H. Diagnosis of colorectal tumorous lesions by magnifying endoscopy. *Gastrointest Endosc*. 1996;44(1):8–14.
- 39 Kida Y, Yamamura T, Maeda K, Sawada T, Ishikawa E, Mizutani Y, et al. Diagnostic performance of endoscopic classifications for neoplastic lesions in patients with ulcerative colitis: A retrospective case-control study. *World J Gastroenterol*. 2022;28(10):1055–66.
- 40 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(10):827–51.
- 41 Kawachi H. Histopathological diagnosis of ulcerative colitis-associated neoplasia. *Dig Endosc*. 2019;31(Suppl 1):31–5.
- 42 Noffsinger AE, Miller MA, Cusi MV, Fenoglio-Preiser CM. The pattern of cell proliferation in neoplastic and nonneoplastic lesions of ulcerative colitis. *Cancer*. 1996;78(11):2307–12.
- 43 Shih IM, Wang TL, Traverso G, Romans K, Hamilton SR, Ben-Sasson S, et al. Top-down morphogenesis of colorectal tumors. *Proc Natl Acad Sci U S A*. 2001;98(5):2640–5.
- 44 Jass JR, Whitehall VL, Young J, Leggett BA. Emerging concepts in colorectal neoplasia. *Gastroenterology*. 2002;123(3):862–76.
- 45 Mikami T, Yoshida T, Akino F, Motoori T, Yajima M, Okayasu I. Apoptosis regulation differs between ulcerative colitis-associated and sporadic colonic tumors. Association with survivin and bcl-2. *Am J Clin Pathol*. 2003;119(5):723–30.
- 46 Ajioka Y, Watanabe H, Matsuda K. Over-expression of p53 protein in neoplastic changes in ulcerative colitis: immunohistochemical study. *J Gastroenterol*. 1995;30(Suppl 8):33–5.
- 47 Ben-Horin S, Izhaki Z, Haj-Natur O, Segev S, Eliakim R, Avidan B. Rarity of adenomatous polyps in ulcerative colitis and its implications for colonic carcinogenesis. *Endoscopy*. 2016;48(3):215–22.

- 48 Sonnenberg A, Genta RM. Low prevalence of colon polyps in chronic inflammatory conditions of the colon. *Am J Gastroenterol*. 2015;110(7):1056–61.
- 49 Dixon A, Wurm P, Hart A, Robinson R. Distal adenomatous polyps are rare in patients with inflammatory bowel disease. *Postgrad Med J*. 2006;82(963):76–8.
- 50 Kitiyakara T, Bailey DM, McIntyre AS, Gorard DA. Adenomatous colonic polyps are rare in ulcerative colitis. *Aliment Pharmacol Ther*. 2004;19(8):879–87.
- 51 Lieberman DA, Weiss DG, Harford WV, Ahnen DJ, Provenzale D, Sontag SJ, et al. Five-year colon surveillance after screening colonoscopy. *Gastroenterology*. 2007;133(4):1077–85.
- 52 Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology*. 2012;143(3):844–57.
- 53 Ninomiya Y, Oka S, Tanaka S, Boda K, Yamashita K, Sumimoto K, et al. Clinical impact of surveillance colonoscopy using magnification without diminutive polyp removal. *Dig Endosc*. 2017;29(7):773–81.
- 54 Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114(3):384–413.
- 55 Farraye FA, Odze RD, Eaden J, Itzkowitz SH. AGA technical review on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. *Gastroenterology*. 2010;138(2):746–74.
- 56 Ng SC, Tang W, Ching JY, Wong M, Chow CM, Hui AJ, et al. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-Pacific Crohn's and colitis epidemiology study. *Gastroenterology*. 2013;145(1):158–165.e2.
- 57 Woolrich AJ, DaSilva MD, Korelitz BI. Surveillance in the routine management of ulcerative colitis: the predictive value of low-grade dysplasia. *Gastroenterology*. 1992;103(2):431–8.

Figure Legends

Fig. 1 Flow chart of the enrolled patients and lesions. SNs in this study were determined by clinical and/ or pathological findings. UC: ulcerative colitis, UCAN: ulcerative colitis-associated neoplasia, SN: sporadic neoplasia, * There is some overlap among the groups

Fig. 2 The site of metachronous SNs according to the site of initial SNs. a) Patients with initial SNs outside the affected range of ulcerative colitis (n=37). b) Patients with initial SNs within the affected range (n=22). SN: sporadic neoplasia

Fig. 3 Kaplan–Meier curves for the cumulative incidence rate of metachronous multiple SNs (n=59), according to a) the number of the initial lesions (single or multiple), b) histology of the initial lesions (carcinoma or adenoma), c) size of the initial lesions (≤ 5 mm or > 5 mm), and d) background mucosa of the lesions (within or outside the affected area). SN: sporadic neoplasia

Research Article
***Characteristics and prognosis of sporadic neoplasias detected in
patients with ulcerative colitis***

Noriko Yamamoto^a, MD, Ken Yamashita^{a*}, MD, PhD, Yudai Takehara^a, MD, Shin Morimoto^a, MD, Fumiaki Tanino^a, MD, Yuki Kamigaichi^a, MD, Hidenori Tanaka^a, MD, PhD, Koji Arihiro^b, MD, PhD, Fumio Shimamoto^c, MD, PhD, Shiro Oka^a, MD, PhD

^a Department of Gastroenterology, Hiroshima University Hospital, Hiroshima, Japan

^b Department of Anatomical Pathology, Hiroshima University Hospital, Hiroshima, Japan

^c Faculty of Health Sciences, Hiroshima Cosmopolitan University, Hiroshima, Japan

Short Title: sporadic neoplasias in patients with ulcerative colitis

*** Corresponding author**

Department of Gastroenterology, Hiroshima University Hospital

1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

Telephone: +81 82 257 5193

Fax: +81 82 257 5194

Email: ken-yama5@hiroshima-u.ac.jp

Keywords: ulcerative colitis, sporadic neoplasia, ulcerative colitis-associated neoplasia, metachronous lesion, characteristics, prognosis

Word count: Main text, 3508 (excluding abstract); Abstract, 243

Abstract

Introduction: Patients with ulcerative colitis (UC) develop not only UC-associated neoplasias but also sporadic neoplasias (SNs). However, few studies have described the characteristics of SNs in patients with UC. Therefore, this study aimed to evaluate the clinical features and prognosis of SNs in patients with UC.

Methods: A total of 141 SNs in 59 patients with UC, detected by surveillance colonoscopy at Hiroshima University Hospital between January 1999 and December 2021, were included. SNs were diagnosed based on their location, endoscopic features, and histopathological findings along with immunohistochemical staining for Ki67 and p53.

Results: Of the SNs, 91.5% were diagnosed as adenoma and 8.5% were diagnosed as carcinoma (Tis carcinoma, 3.5%; T1 carcinoma, 5.0%). Most lesions (61.0%) were located in the right colon, 31.2% were located in the left colon, and 7.8% were located in the rectum. When classified based on site of lesion, 70.9% of SNs occurred outside and 29.1% within the affected area. Of all SNs included, 95.7% were endoscopically resected and 4.3% were surgically resected. Among the 59 patients included, synchronous SNs occurred in 23.7% and metachronous multiple SNs occurred in 40.7% during surveillance. The 5-year cumulative incidence of metachronous multiple SNs was higher in patients with synchronous multiple SNs (54.2%) than in those without synchronous multiple SNs (46.4%).

Conclusion: Patients with UC with synchronous multiple SNs are at a higher risk of developing metachronous multiple SNs and may require closer follow-up by total colonoscopy than patients without synchronous SNs.

Introduction

Recently, the prevalence of ulcerative colitis (UC) has been increasing worldwide [1, 2]. However, the need for colectomy in patients with refractory disease has been decreasing as recent advances in UC treatment have led to an increasing proportion of patients achieving remission [3-5]. Moreover, the number of surgeries for UC-associated dysplasia (UCAD)/UC-associated carcinoma (UCAC) is increasing [5]. UC-associated neoplasias (UCANs) are known to develop in patients with long-standing UC [6, 7]. Additionally, sporadic neoplasias (SNs) are also detected in patients with UC [8].

Total proctocolectomy is recommended as the standard procedure for patients with UCAC or high-grade dysplasia (HGD) [9–11], because approximately 43%–50% of them may have concomitant malignancies at the time of colectomy [12–15]. In contrast, the management of low-grade dysplasia (LGD) in patients with UC remains controversial [10, 11]. The Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations (SCENIC) statement suggests that LGDs can be resected endoscopically if they are endoscopically visible [16]. However, there is no clear consensus regarding the treatment method for endoscopically invisible dysplasia [17]. Although the reported progression rate from LGD to HGD or carcinoma varies from 0%–53% [18-21], the presence of LGD is a risk factor for higher-grade neoplasia. Proctocolectomy eliminates the risk of colorectal carcinoma (CRC) in patients with UC-associated LGD. However, the decision to perform proctocolectomy or continued surveillance in patients with flat and endoscopically invisible LGD should be individualized and discussed between the patient, gastroenterologist, and colorectal surgeon [9, 22]. In contrast, SNs have a better prognosis than UCANs [23, 24] and are good indicators for local excision by endoscopic resection (ER) or partial colectomy, even in patients with UC [8, 9, 25]. The SCENIC statement recommends ER and surveillance colonoscopy (SCS) for polypoid lesions [16]; however, it does not clearly distinguish UCANs from SNs [16]. On the other hand, the European Crohn's and Colitis Organisation (ECCO) consensus on the diagnosis and management of UC describes that polypoid dysplasia could be adequately treated by polypectomy if the lesion can be completely excised and there is no evidence of non-polypoid or invisible dysplasia elsewhere in the colon [9]. Furthermore, sporadic adenomas in patients with UC are also suggested to be treated as in patients without UC in this statement.

However, sporadic adenoma is defined as a polyp occurring in an area proximal to the microscopic level of inflammation, with no dysplasia in the flat mucosa [9]. Although various studies have been conducted on UCANs, they did not strictly distinguish between UCAN and SN in patients with UC [24, 26, 27]. Therefore, this study aimed to evaluate the clinical features and prognosis of SNs in patients with UC.

Methods

Ethics statements

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the Hiroshima University Hospital (approval number: E2022-0318; registration date: May 12, 2023). All patients provided written informed consent before participation.

Patients

In total, 974 patients with UC who underwent endoscopic or surgical resection at the Hiroshima University Hospital between January 1999 and December 2021 were included. Of them, we retrospectively reviewed the medical records of 143 consecutive patients with 300 neoplasias detected using SCS. We excluded 75 patients with 99 UCANs diagnosed from resected specimens and 47 patients with 60 serrated lesions. This is because serrated lesions progress to CRCs through the serrated neoplasia pathway, which is different from the adenoma-carcinoma pathway [28, 29]. Finally, 59 patients with UC and 141 SNs were enrolled (Figure 1). No patient had concurrent UCAN at the time of initial SN detection. However, one patient developed UCANs during the follow-up period after the initial SN diagnosis. Although this patient and the SNs that occurred in this patient were included, the UCANs that occurred in this patient were excluded from this study. In this study, SNs detected within 2 months of the initial SN detection were defined as synchronous SNs, and those detected 2 months after the initial SN detection were defined as metachronous SNs [30, 31].

Endoscopic examination

In principle, we perform total colonoscopy (TCS) annually for patients with UC with left-sided or total colitis and a disease duration of > 7 years, if possible, in the remission stage. Endoscopists with at least 5 years of endoscopic and 1000 colonoscopies experience performed SCS for patients with UC. We also perform step and target biopsies. Step biopsy is performed by collecting a sample from each segment: the terminal ileum, ascending colon, transverse colon, descending colon, sigmoid colon, Ra (upper rectum), and Rb (lower rectum). Target biopsy is performed for lesions with features that indicate UCAN, such as slight elevation/depression of the mucosa, focal friability, obscure vascular pattern, discoloration (slight redness or paleness), villous mucosa (velvety appearance), or irregular nodularity [32, 33]. In addition, when a lesion (UCAN or SN) is detected, we perform a biopsy from

the mucosa near the lesion. In this study, we used the term "within the affected mucosa" when the histopathological findings of the biopsy from the mucosa near the lesion showed active inflammation or post-inflammatory changes (crypt architectural distortion or atrophy) [34], and "outside the affected mucosa" in other cases. All colorectal lesions were investigated using white light and narrowband imaging and/or chromo-magnification (indigo carmine). Additional magnifying observations with crystal violet were performed for colorectal lesions with irregular pit patterns. According to the Kudo-Tsuruta classification, lesions are categorized as having type I, II, IIIL, IIIS, IV, VI, or VN pit patterns [35].

Indication for treatment

Neoplasias within the UC-affected area can be UCANs or SNs. In contrast, neoplasias outside the UC-affected area are definite SNs. However, the UC-affected area sometimes extends more proximally, making it difficult to detect neoplasias within the UC-affected area. Therefore, we resected all neoplasias in patients with UC unless the patient was in poor general condition or refused to undergo neoplasia resection. The lesions outside the affected area were treated as SNs in non-UC patients: ER for lesions suspected of adenomas, mucosal carcinomas, or superficial submucosal invasive carcinomas and partial colectomy for lesions suspected of carcinomas invading the deep submucosal layer or deeper. For lesions within the affected area, ER was performed if the lesion was endoscopically well-defined, and no dysplasia was detected using biopsy from four points on the surrounding mucosa. The lesions with endoscopically indistinct borders or with dysplasias in the surrounding mucosa were considered UCANs and excluded from this study. The final diagnosis of UCAN or SN was based on the findings of resected specimens. Total colectomy was performed for UCANs diagnosed as carcinoma or HGD on biopsy of the pre-treatment lesion. For UCANs diagnosed as LGD on biopsy from a pretreatment lesion with an endoscopically indistinct border, the decision to perform total colectomy or close follow-up was discussed among several experienced physicians and gastrointestinal pathologists.

Histopathological assessment

All resected specimens were fixed in 10% formalin, sliced into 2-mm sections, embedded in paraffin, serially sectioned, stained with hematoxylin and eosin, and examined microscopically. The histopathological diagnosis of SNs was made according to the World Health Organization classification system [36]. The depth of submucosal invasion was determined on the basis of the

Japanese Society for the Colon and Rectum Classification [31]. Accordingly, lesions were classified as adenomas (including tubular adenoma, tubulovillous adenoma, and villous adenoma), Tis carcinoma (intramucosal carcinoma), T1a carcinoma (superficially submucosal invasive carcinoma: submucosal invasive depth < 1000 μ m), or T1b carcinoma (deeply submucosal invasive carcinoma: submucosal invasive depth \geq 1000 μ m) [31]. In all cases, the histopathological diagnosis of the resected lesions was confirmed and reviewed by more than one gastrointestinal pathologist.

Immunohistochemical evaluation of Ki67 and p53 expressions was performed to distinguish between UCANs and SNs. In UCANs, Ki67-positive cells are mainly found at the basal side of the mucosa, and tumor cells differentiate towards the superficial side of the mucosa, which is the “bottom-up morphology.” Conversely, in SNs, particularly in conventional tubular adenomas, Ki67-positive cells are mainly found at the superficial zone of the mucosal layer, and tumor cells differentiate towards the basal side of the mucosa, which is the “top-down morphology.” Additionally, UCANs show a significantly higher degree of p53 expression than sporadic adenomas [37], which is also useful to differentiate between UCANs and SNs. In cases where it was difficult to differentiate between SNs and UCANs, the final diagnosis was established by at least two expert pathologists (KA and FS).

Investigated variables

The patients’ clinicopathological characteristics (age, sex, UC duration, type of UC, clinical course, and presence or absence of synchronous multiple lesions) and clinicopathological features of the SNs (tumor location, background mucosa, tumor size, color, gross type, pit pattern [38], histology, and treatment method) were evaluated. Additionally, the development of metachronous multiple SNs after the first SN detection as the long-term prognosis according to the number, histology, size, and background mucosa of the initial lesions was evaluated.

Statistical analysis

Data are expressed as mean \pm standard deviation, median with range, or percentages. The incidence rate of metachronous lesions after the initial SNs was calculated using the Kaplan–Meier method. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using JMP software, version 16 (SAS Institute, Cary, NC, USA).

Results

The clinical features of the enrolled patients are presented in Table 1. The mean age at the first SN detection was 58.8 years, and the median duration of UC was 7 years. Males comprised 64.4% of the enrolled patients. The most common UC type was total colitis (47.5%). Regarding their clinical course, 49.2% of patients presented with the relapse-remitting type, 23.7% with the chronic continuous type, and 27.1% with the first attack type. Of the 59 patients, 23.7% had multiple SNs during the first detection. Metachronous multiple SNs occurred in 40.7% of the patients. Furthermore, 14 patients had synchronous SNs at initial SN detection, and 24 developed metachronous SNs during the follow-up period after initial SN detection.

The clinicopathological features of the enrolled lesions are presented in Table 2. SNs occurred in 61.0% of patients in the right colon, 31.2% in the left colon, and 7.8% in the rectum. When classified as outside or within the affected area of UC, 70.9% of SNs occurred outside and 29.1% within the affected area. Metachronous SNs tended to occur outside the affected area if the initial lesions were located outside the affected area. Whereas if the initial lesions were located within the affected area, metachronous SNs tended to occur both outside and inside the affected area (Figure 2). The mean tumor size was 5.8 mm. The color was reddish in 21.3% of the lesions and normal in 78.7%. The gross tumor type was protruded in 73.1% of the lesions and superficial in 26.9%. Additionally, we assessed the pit patterns of the lesions. Overall, 86.5% of the lesions were classified as type III-L, 10.7% as type VI (5 adenomas, 4 Tis carcinomas, and 6 T1 carcinomas), and only 0.7% as type VN (1 T1 carcinoma).

The frequency of adenomas among all SNs was 91.5%; that of Tis and T1 carcinoma was 3.5% and 5.0%, respectively. Among the 141 SNs, 135 (95.7%) were endoscopically resected (endoscopic mucosal resection or endoscopic submucosal dissection). Partial colectomy was performed in only six lesions (4.3%), of which five were T1b carcinomas and the remaining was an adenoma close to a T1b carcinoma.

The clinicopathological features of the carcinomas are presented in Table 3. Lesion numbers (nos.) 3 and 4 were synchronous carcinomas detected in the same patient. Of the 12 sporadic carcinomas in 11 patients, five lesions occurred within 1 year after the onset of UC. **All sporadic carcinomas had adenoma components and were diagnosed as sporadic based on the expression patterns of Ki67 and p53 in the adenoma component.** Most UC cases were of total colitis (7/12 cases). Half of the lesions occurred outside the affected area, and half within the affected area. Most of the lesions (10/12 cases) were reddish. All T1b carcinomas were surgically resected, whereas T1a and Tis carcinomas were endoscopically resected. Of the 11 patients, four (lesions nos. 3, 4, 7, 9, and 12) had synchronous SNs at the time of carcinoma detection. Metachronous SNs after carcinomas occurred in three patients (lesions nos. 2, 7, and 12). Only the patient with lesion no. 9 had metachronous

adenomas before the carcinoma (lesion no. 9) occurred, and the prior lesions were a 6-mm and 5-mm adenoma, both of which were resected endoscopically.

Figure 3 illustrates the Kaplan–Meier curves for the cumulative incidence rate of metachronous SNs. The histology, size, and background mucosa of the initial lesions were not associated with the incidence of metachronous lesions. The 5-year and 10-year cumulative incidence rate of metachronous multiple SNs were significantly higher in patients with synchronous multiple SNs than in those without (61% and 82% versus [vs.] 42% and 51%).

Discussion

Our data showed that SNs in patients with UC were more likely to occur outside the affected mucosa than within, and that patients with multiple SNs at the time of initial SN detection were more likely to develop multiple metachronous lesions in subsequent years. Furthermore, half of the SNs occurred within 7 years of UC onset, suggesting that SNs can occur earlier than UCANs. Therefore, the SCS method for detecting UCANs and SNs in patients with UC requires reconsideration. UCANs occur only within the affected area of UC, whereas SNs occur both outside and within the affected area [8, 39]. Moreover, the differences in the characteristics and prognoses between CAC in patients with UC and sporadic CRC in patients without UC have been assessed in several previous studies; patients with CAC and UC had younger age at carcinoma diagnosis, higher rate of synchronous multiple lesions and mucinous/signet ring cell carcinomas, and poorer prognosis [24, 26, 27]. However, limited studies have been conducted on the features and prognosis of sporadic adenoma/carcinoma, particularly within the affected area [8].

Recent ECCO histopathological statements have indicated that some pathological features help differentiate UCANs from SNs; associated flat dysplasia (no sharp delineation), irregular neoplastic glands (varying configuration, size, and diameter) with varying amounts of stroma, increased (mononuclear) lamina propria inflammation, and a mixture of benign/dysplastic crypts at the surface [40]. Furthermore, recent studies have shown that immunohistochemistry also helps differentiate UCANs from SNs. Evaluation of the proliferative zone is considered particularly useful for the differential diagnosis of UC-associated LGD and low-grade sporadic adenoma [25, 41]. Although the results of such evaluations are not always conclusive, the distribution of Ki67-positive cells in the mucosa is one of the useful findings to distinguish UCANs from SNs [25, 40, 41]. In non-neoplastic mucosa, Ki67-staining is restricted to the basal third of the crypt. However, Ki67-staining expands to the upper epithelium in dysplasias. Moreover, in some dysplasias and all invasive carcinomas, Ki67-

staining is diffusely distributed throughout the crypts [42]. In contrast, Ki67-positive cells are mainly distributed to the upper side of the epithelium in sporadic adenoma [43, 44]. Similar to UCAC, sporadic carcinoma shows diffuse contributions of Ki67-positive cells [45]. Regarding UCANs, most lesions show diffuse and strong expression of p53 and the occasional null expression of p53. However, in intramucosal lesions, such as LGD, p53 expression is not universal but is mainly distributed at the basal side of the crypts [25, 41, 46]. In contrast, most SNs show weaker p53 expression than UCANs, although some SNs show strong p53 expression, especially in high-grade lesions [37]. Some UCANs also have a surrounding flat area with p53 overexpression, which is absent in SNs that instead have a distinct border between the neoplastic glands and the surrounding mucosa [8, 25].

The terms “dysplasia-associated lesion or mass,” “adenoma-like,” and “non-adenoma-like” were abandoned in the SCENIC statement. Instead, classification according to the lesion morphology was recommended; however, this classification does not distinguish UCANs from SNs [16]. Therefore, both UC-associated and sporadic polypoid lesions within the UC-affected area in patients with UC fall into the same category. Nonetheless, it is important to distinguish between UCANs and SNs because they have different prognoses and require varied treatment strategies [40]. Hence, we evaluated only endoscopically or surgically resected lesions and divided them into UCANs and SNs based on endoscopic findings and histopathology with immunohistochemical staining. The majority of the enrolled SNs were diagnosed as adenomas (91.5%). Moreover, there were no advanced-stage carcinomas in this study, which may be because patients with UC undergo SCS more frequently than non-UC patients, essentially every year in our hospital.

Several reports have described the low prevalence of adenomatous polyps in patients [47-50]. However, one study also showed that the rate of adenomatous sporadic polyps outside the affected area in patients with UC was not different from that in patients without UC (13.1% vs. 13.4%) [47].

Regarding patients without UC, the National Polyp Study Workgroup reported that the risk of metachronous lesions differs according to the size, number, or histology of the initial lesions [51]. According to the United States guidelines published in 2012 [52], the interval for colonoscopy after screening and ER is defined based on the characteristics of the resected lesions namely, size (< 10 mm/≥ 10 mm), number (1–2/3–10/≥ 11), and histopathology (tubular adenoma/villous adenoma/sessile serrated polyp/traditional serrated adenoma) of lesions. The British guidelines in 2010 [22] also recommended a similar SCS method after ER based on the number or size of polyps detected during the initial colonoscopy. Furthermore, our institution previously reported that male sex, multiple lesions at initial colonoscopy, and carcinoma at initial colonoscopy were the relative risk

factors for the incidence of a lesion indicated for ER in the non-UC population [53]. In contrast, in this study, we found that patients with UC with multiple SNs at the time of initial SN detection had a higher rate of subsequent metachronous multiple lesions than patients with UC with only one initial lesion, similar to the characteristics of neoplasias in non-UC patients. However, patient sex, lesion histology, tumor size, and lesion site were not associated with the incidence of metachronous lesions in our study. Although approximately half of the enrolled lesions developed outside the UC-affected area and half developed within the UC-affected area, metachronous lesions after the first SNs tended to develop outside the affected area, particularly when the first lesions occurred in the unaffected area.

Recent guidelines have suggested some SCS strategies for patients with UC, such as performing SCS for patients with left-sided colitis or total colitis with a UC duration of 8–10 years or more, because they have a higher CRC risk than non-UC patients. In contrast, patients with ulcerative proctitis are not indicated for SCS because they have similar CRC risks to non-UC patients [9, 54, 55]. However, these strategies focus on reducing UCAC-associated morbidity and mortality. Approximately two-thirds of the patients with UC have left-sided colitis or proctitis [56], and most UCANs occur in the left-sided colon, particularly in the rectum and sigmoid colon [21, 24, 57]. Therefore, several studies used sigmoidoscopy as a surveillance tool for UC [49, 57]. However, patients with UC also develop SNs, not only UCANs. Additionally, as our results demonstrated, SNs occur both within and outside the UC-affected area. This suggests an insufficiency of sigmoidoscopy and the need for TCS to detect SNs in patients with UC. Furthermore, the present data suggested that SCS for patients with UC with multiple SNs should be performed according to the colorectal polyp guidelines for non-UC patients, even if they have proctitis-type UC or have UC duration for < 8 years, although several guidelines for inflammatory bowel disease recommend periodic SCS only for patients with left-sided or total colitis-type UC with UC duration > 8–10 years [9, 10, 54, 55] and not for patients with proctitis-type UC or UC duration < 8 years.

Nonetheless, this study had some limitations. First, this study included only a few carcinomas, and therefore did not adequately assess the characteristics and prognosis of carcinomas. Further data is required to evaluate the characteristics and prognosis of carcinomas. Second, because mucosal inflammation complicates recognition of tumor margins, SNs within the inflamed mucosa could have been missed, especially for small lesions, and not all SNs, including small adenomas, could have been evaluated. To avoid missing lesions within the inflammatory mucosa, it is necessary to aim for more mucosal quiescence of UC and to perform SCS during the remission phase. In addition, it is possible that some small adenomas were missed at the initial SCS and mistakenly included as

279 metachronous SNs. This may suggest that the cumulative incidence of metachronous SNs may be
280 overestimated. Finally, this was a single-center retrospective study conducted in a tertiary care
281 center; therefore, the results of this study may not be generalizable to the entire population of
282 patients with UC.

283 In conclusion, attention should be paid to the occurrence of SNs as well as UCANs, even in
284 patients with UC. Both affected and unaffected areas should be screened, regardless of the degree or
285 extent of UC inflammation to detect SNs, along with careful surveillance using TCS, particularly in
286 patients with UC with multiple SNs, because they tend to develop new lesions.

287

Statements

Statement of Ethics

Ethical approval: This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the Hiroshima University Hospital (approval number: E2022-0318; registration date: May 12, 2023).

Consent to participate: All patients were informed of the risks and benefits of colonoscopy and provided written informed consent before participation.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

Study design: Shiro Oka, Ken Yamashita, and Noriko Yamamoto. Sample collection: Noriko Yamamoto, Ken Yamashita, Yudai Takehara, Shin Morimoto, Fumiaki Tanino, Yuki Kamigaichi, and Hidenori Tanaka. Sample evaluation: Koji Arihiro and Fumio Shimamoto. Data collection: Noriko Yamamoto. Data analysis: Noriko Yamamoto. Manuscript writing: Noriko Yamamoto and Ken Yamashita. All authors have read and approved the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are not openly available due to the privacy of patients and are available from the corresponding author upon reasonable request. Data are in controlled access data storage at Hiroshima University Hospital.

References

- 1 Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet*. 2017;390(10114):2769–78.
- 2 Kaplan GG, Ng SC. Understanding and preventing the global increase of inflammatory bowel disease. *Gastroenterology*. 2017;152(2):313–321.e2.
- 3 Eriksson C, Cao Y, Rundquist S, Zhulina Y, Henriksson I, Montgomery S, et al. Changes in medical management and colectomy rates: a population-based cohort study on the epidemiology and natural history of ulcerative colitis in Örebro, Sweden, 1963–2010. *Aliment Pharmacol Ther*. 2017;46(8):748–57.
- 4 Noguchi T, Ishihara S, Uchino M, Ikeuchi H, Okabayashi K, Futami K, et al. Clinical features and oncological outcomes of intestinal cancers associated with ulcerative colitis and Crohn’s disease. *J Gastroenterol*. 2023;58(1):14–24.
- 5 Uchino M, Ikeuchi H, Hata K, Okada S, Ishihara S, Morimoto K, et al. Changes in the rate of and trends in colectomy for ulcerative colitis during the era of biologics and calcineurin inhibitors based on a Japanese nationwide cohort study. *Surg Today*. 2019;49(12):1066–73.
- 6 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(6):639–45.
- 7 Colman RJ, Rubin DT. Histological inflammation increases the risk of colorectal neoplasia in ulcerative colitis: a systematic review. *Intest Res*. 2016;14(3):202–10.
- 8 Mutaguchi M, Naganuma M, Sugimoto S, Fukuda T, Nanki K, Mizuno S, et al. Difference in the clinical characteristic and prognosis of colitis-associated cancer and sporadic neoplasia in ulcerative colitis patients. *Dig Liver Dis*. 2019;51(9):1257–64.
- 9 Magro F, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: Definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. *J Crohns Colitis*. 2017;11(6):649–70.
- 10 Matsuoka K, Kobayashi T, Ueno F, Matsui T, Hirai F, Inoue N, et al. Evidence-based clinical practice guidelines for inflammatory bowel disease. *J Gastroenterol*. 2018;53(3):305–53.

- 11 Ross H, Steele SR, Varma M, Dykes S, Cima R, Buie WD, et al. Practice parameters for the surgical treatment of ulcerative colitis. *Dis Colon Rectum*. 2014;57(1):5–22.
- 12 Bernstein CN, Shanahan F, Weinstein WM. Are we telling patients the truth about surveillance colonoscopy in ulcerative colitis? *Lancet*. 1994;343(8889):71–4.
- 13 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(2):366–74.
- 14 Riddell RH, Goldman H, Ransohoff DF, Appelman HD, Fenoglio CM, Haggitt RC, et al. Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. *Hum Pathol*. 1983;14(11):931–68.
- 15 Torres C, Antonioli D, Odze RD. Polypoid dysplasia and adenomas in inflammatory bowel disease: a clinical, pathologic, and follow-up study of 89 polyps from 59 patients. *Am J Surg Pathol*. 1998;22(3):275–84.
- 16 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(3):489–501.e26.
- 17 Shah SC, Itzkowitz SH. Colorectal cancer in inflammatory bowel disease: mechanisms and management. *Gastroenterology*. 2022;162(3):715–730.e3.
- 18 Befrits R, Ljung T, Jaramillo E, Rubio C. Low-grade dysplasia in extensive, long-standing inflammatory bowel disease: a follow-up study. *Dis Colon Rectum*. 2002;45(5):615–20.
- 19 Lim CH, Dixon MF, Vail A, Forman D, Lynch DAF, Axon ATR. Ten year follow up of ulcerative colitis patients with and without low grade dysplasia. *Gut*. 2003;52(8):1127–32.
- 20 Connell WR, Lennard-Jones JE, Williams CB, Talbot IC, Price AB, Wilkinson KH. Factors affecting the outcome of endoscopic surveillance for cancer in ulcerative colitis. *Gastroenterology*. 1994;107(4):934–44.
- 21 Ullman T, Croog V, Harpaz N, Sachar D, Itzkowitz S. Progression of flat low-grade dysplasia to advanced neoplasia in patients with ulcerative colitis. *Gastroenterology*. 2003;125(5):1311–9.
- 22 Cairns SR, Scholefield JH, Steele RJ, Dunlop MG, Thomas HJ, Evans GD, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). *Gut*. 2010;59(5):666–89.

- 23 Annese 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(11):945–65.
- 24 Watanabe T, Konishi T, Kishimoto J, Kotake K, Muto T, Sugihara K, et al. Ulcerative colitis-associated colorectal cancer shows a poorer survival than sporadic colorectal cancer: a nationwide Japanese study. *Inflam Bowel Dis*. 2011;17(3):802–8.
- 25 Vieth M, Behrens H, Stolte M. Sporadic adenoma in ulcerative colitis: endoscopic resection is an adequate treatment. *Gut*. 2006;55(8):1151–5.
- 26 Jensen AB, Larsen M, Gislum M, Skriver MV, Jepsen P, Nørgaard B, et al. Survival after colorectal cancer in patients with ulcerative colitis: a nationwide population-based Danish study. *Am J Gastroenterol*. 2006;101(6):1283–7.
- 27 Leowardi C, Schneider ML, Hinz U, Harnoss JM, Tarantino I, Lasitschka F, et al. Prognosis of ulcerative colitis-associated colorectal carcinoma compared to sporadic colorectal carcinoma: A matched pair analysis. *Ann Surg Oncol*. 2016;23(3):870–6.
- 28 Noffsinger AE. Serrated polyps and colorectal cancer: new pathway to malignancy. *Annu Rev Pathol*. 2009;4:343–64.
- 29 Kambara T, Simms LA, Whitehall VLJ, Spring KJ, Wynter CV, Walsh MD, et al. BRAF mutation is associated with DNA methylation in serrated polyps and cancers of the colorectum. *Gut*. 2004;53(8):1137–44.
- 30 National Cancer Institute, Surveillance, Epidemiology and End Results Program, Bethesda MD. The 2007 multiple primary and histology coding rules; 2007.
- 31 Japanese Society for Cancer of the Colon and Rectum. Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma: the 3-d. English ed. Secondary Publication. *J Anus Rectum Colon*; 2019;3(4):175-95.
- 32 Oka S, Tanaka S, Chayama K. Detection of nonpolypoid colorectal neoplasia using magnifying endoscopy in colonic inflammatory bowel disease. *Gastrointest Endosc Clin N Am*. 2014;24(3):405–17.
- 33 Oka S, Uraoka T, Watanabe K, Hata K, Kawasaki K, Mizuno K, et al. Endoscopic diagnosis and treatment of ulcerative colitis-associated neoplasia. *Dig Endosc*. 2019;31(Suppl 1):26–30.
- 34 Gheorghe C, Cotruta B, Iacob R, Becheanu G, Dumbrava M, Gheorghe L. Endomicroscopy for assessing mucosal healing in patients with ulcerative colitis. *J Gastrointest Liver Dis*. 2011;20(4):423–6.

- 35 Kudo S, Hirota S, Nakajima T, Hosobe S, Kusaka H, Kobayashi T, et al. Colorectal tumours and pit pattern. *J Clin Pathol*. 1994;47(10):880–5.
- 36 Boman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO classification of tumours of the digestive system. 4th ed. Lyon, France: IARC; 2010.
- 37 Walsh SV, Loda M, Torres CM, Antonioli D, Odze RD. P53 and beta catenin expression in chronic ulcerative colitis-associated polypoid dysplasia and sporadic adenomas: an immunohistochemical study. *Am J Surg Pathol*. 1999;23(8):963–9.
- 38 Kudo S, Tamura S, Nakajima T, Yamano H, Kusaka H, Watanabe H. Diagnosis of colorectal tumorous lesions by magnifying endoscopy. *Gastrointest Endosc*. 1996;44(1):8–14.
- 39 Kida Y, Yamamura T, Maeda K, Sawada T, Ishikawa E, Mizutani Y, et al. Diagnostic performance of endoscopic classifications for neoplastic lesions in patients with ulcerative colitis: A retrospective case-control study. *World J Gastroenterol*. 2022;28(10):1055–66.
- 40 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(10):827–51.
- 41 Kawachi H. Histopathological diagnosis of ulcerative colitis-associated neoplasia. *Dig Endosc*. 2019;31(Suppl 1):31–5.
- 42 Noffsinger AE, Miller MA, Cusi MV, Fenoglio-Preiser CM. The pattern of cell proliferation in neoplastic and nonneoplastic lesions of ulcerative colitis. *Cancer*. 1996;78(11):2307–12.
- 43 Shih IM, Wang TL, Traverso G, Romans K, Hamilton SR, Ben-Sasson S, et al. Top-down morphogenesis of colorectal tumors. *Proc Natl Acad Sci U S A*. 2001;98(5):2640–5.
- 44 Jass JR, Whitehall VL, Young J, Leggett BA. Emerging concepts in colorectal neoplasia. *Gastroenterology*. 2002;123(3):862–76.
- 45 Mikami T, Yoshida T, Akino F, Motoori T, Yajima M, Okayasu I. Apoptosis regulation differs between ulcerative colitis-associated and sporadic colonic tumors. Association with survivin and bcl-2. *Am J Clin Pathol*. 2003;119(5):723–30.
- 46 Ajioka Y, Watanabe H, Matsuda K. Over-expression of p53 protein in neoplastic changes in ulcerative colitis: immunohistochemical study. *J Gastroenterol*. 1995;30(Suppl 8):33–5.
- 47 Ben-Horin S, Izhaki Z, Haj-Natur O, Segev S, Eliakim R, Avidan B. Rarity of adenomatous polyps in ulcerative colitis and its implications for colonic carcinogenesis. *Endoscopy*. 2016;48(3):215–22.

- 48 Sonnenberg A, Genta RM. Low prevalence of colon polyps in chronic inflammatory conditions of the colon. *Am J Gastroenterol*. 2015;110(7):1056–61.
- 49 Dixon A, Wurm P, Hart A, Robinson R. Distal adenomatous polyps are rare in patients with inflammatory bowel disease. *Postgrad Med J*. 2006;82(963):76–8.
- 50 Kitiyakara T, Bailey DM, McIntyre AS, Gorard DA. Adenomatous colonic polyps are rare in ulcerative colitis. *Aliment Pharmacol Ther*. 2004;19(8):879–87.
- 51 Lieberman DA, Weiss DG, Harford WV, Ahnen DJ, Provenzale D, Sontag SJ, et al. Five-year colon surveillance after screening colonoscopy. *Gastroenterology*. 2007;133(4):1077–85.
- 52 Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology*. 2012;143(3):844–57.
- 53 Ninomiya Y, Oka S, Tanaka S, Boda K, Yamashita K, Sumimoto K, et al. Clinical impact of surveillance colonoscopy using magnification without diminutive polyp removal. *Dig Endosc*. 2017;29(7):773–81.
- 54 Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114(3):384–413.
- 55 Farraye FA, Odze RD, Eaden J, Itzkowitz SH. AGA technical review on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. *Gastroenterology*. 2010;138(2):746–74.
- 56 Ng SC, Tang W, Ching JY, Wong M, Chow CM, Hui AJ, et al. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-Pacific Crohn's and colitis epidemiology study. *Gastroenterology*. 2013;145(1):158–165.e2.
- 57 Woolrich AJ, DaSilva MD, Korelitz BI. Surveillance in the routine management of ulcerative colitis: the predictive value of low-grade dysplasia. *Gastroenterology*. 1992;103(2):431–8.

Figure Legends

Fig. 1 Flow chart of the enrolled patients and lesions. SNs in this study were determined by clinical and/ or pathological findings. UC: ulcerative colitis, UCAN: ulcerative colitis-associated neoplasia, SN: sporadic neoplasia, * There is some overlap among the groups

Fig. 2 The site of metachronous SNs according to the site of initial SNs. a) Patients with initial SNs outside the affected range of ulcerative colitis (n=37). b) Patients with initial SNs within the affected range (n=22). SN: sporadic neoplasia

Fig. 3 Kaplan–Meier curves for the cumulative incidence rate of metachronous multiple SNs (n=59), according to a) the number of the initial lesions (single or multiple), b) histology of the initial lesions (carcinoma or adenoma), c) size of the initial lesions (≤ 5 mm or > 5 mm), and d) background mucosa of the lesions (within or outside the affected area). SN: sporadic neoplasia

Editor-in-Chief comments :

This is an interesting study. Furthermore, several concerns are pointed out. Without any commitment for acceptance, we would be pleased to reconsider revised version of your manuscript which takes into account the reviewers' comments. Submitting a revision of your manuscript does not guarantee eventual acceptance.

Associate Editor comments :**Comments to authors:****Reviewer 1**

The author demonstrated the Characteristics and prognosis of sporadic neoplasias detected in patients with ulcerative colitis. This is very interesting and important study. There are several points to be revised.

1. There is a lack of information regarding the endoscopist who performed the endoscopy. Years of experience and number of endoscopies performed need to be included.

-> Thank you for your pertinent comment. We have added the following text to the Methods section (page 4, lines 77–78):

Endoscopists with at least 5 years of endoscopic and 1000 colonoscopies experience performed SCS for patients with UC.

2. The definitions of “Outside the affected mucosa” and “Within the affected mucosa” are unclear. A clear definition of each mucosa is needed.

-> Thank you for your pertinent comment. In order to clearly define “outside the affected mucosa” and “within the affected mucosa”, we have added another reference paper [34] to the References section and the following text to the Methods section (page 4–5, lines 84–88):

In addition, when a lesion (UCAN or SN) is detected, we perform a biopsy from the mucosa near the lesion. In this study, we used the term "within the affected mucosa" when the histopathological findings of the biopsy from the mucosa near the lesion showed active inflammation or post-inflammatory changes (crypt architectural distortion or atrophy) [34], and "outside the affected mucosa" in other cases.

3. A description of the patient's medication is required in Table 1.

-> Thank you for your pertinent comment. We have added the use of aminosalicylates, azathioprine, corticosteroids, tacrolimus, anti-TNF- α agents, and integrin inhibitors as the treatment history for patients with UC in Table 1.

Reviewer 2

The authors conducted a retrospective observational study to investigate the clinical features and prognosis of sporadic neoplasias (SNs) in patients with ulcerative colitis. This paper is well written, and the authors carefully presented their data. However, the strengths of this paper are unclear and seem to have little impact.

1. The authors showed the significantly higher cumulative incidence rate of metachronous SNs in patients with UC who have multiple lesions at initial colonoscopy. The authors mentioned that the surveillance colonoscopy (SCS) method in patients with UC requires reconsideration. What is the best interval for colonoscopy in patients with UC? Does these data have any impact on the current recommendation for annual surveillance colonoscopy in patients with UC?

-> Thank you for pertinent question. We have added the following text to the Discussion section to better explain these aspects (page 10, lines 265–270):

Furthermore, the present data suggested that SCS for patients with UC with multiple SNs should be performed according to the colorectal polyp guidelines for non-UC patients, even if they have proctitis-type UC or have UC duration for < 8 years, although several guidelines for inflammatory bowel disease recommend periodic SCS only for patients with left-sided or total colitis-type UC with UC duration > 8–10 years [9, 10, 54, 55] and not for patients with proctitis-type UC or UC duration < 8 years.

2. Are there any difference in the histologic features between SNs outside the UC-affected area and those within the affected area?

-> Thank you for your pertinent question. In this study, pathology of all resected lesions was confirmed and reviewed by more than one gastrointestinal pathologist, and no differences in

the histologic features were noted between SNs outside the UC-affected area and those within the affected area.

3. UCADs (line 120 at Page 7) seems wrong. I think UCANs is correct.

-> Thank you for pointing this out. We have revised “UCADs” to “UCANs”. (page 6, line 128)

Reviewer 3

In this manuscript, the authors investigated the clinical features and prognosis of sporadic neoplasias (SNs) in patients with ulcerative colitis (UC). They concluded that attention should be paid to the occurrence of SNs as well as UC-associated neoplasias (UCANs), particularly in patients with UC with multiple SNs, because they tend to develop new lesions. This study is interesting because few studies have described the characteristics of SNs in patients with UC. However, some improvements can still be made to improve the clarity of the contribution.

Major comments

1. Figure 3a shows that in all cases of patients with synchronous multiple SNs at initial colonoscopy, metachronous SNs occurred within 2 years. This is too short a period of time for new SNs to have occurred, and it is possible that the lesions were missed at initial colonoscopy. This should be mentioned in the discussion section.

-> Thank you for valuable comment. We have added the following text in the Discussion section. (page 10–11, lines 277–280):

In addition, it is possible that some small adenomas were missed at the initial SCS and mistakenly included as metachronous SNs. This may suggest that the cumulative incidence of metachronous SNs may be overestimated.

In addition, there does not seem to be much difference in the incidence of metachronous multiple SNs between patients with multiple lesions at initial colonoscopy and patients with single lesions at initial colonoscopy, five years after the initial examination. From these considerations, the authors conclude that the study “Patients with UC with synchronous multiple SNs are at a higher risk of developing metachronous multiple SNs and may require closer follow-up by total colonoscopy than patients without synchronous SNs.”, which, in my opinion, seems an undesirable conclusion.

-> Thank you for your pertinent comment. When we examined the incidence of metachronous SNs within 5 years and after ≥ 5 years, the cumulative incidence rate of metachronous SNs was constantly greater in patients with multiple SNs at initial colonoscopy than in those with a single SN.

We have changed the graphs in Figure 3 to include the ≥ 5 years after initial colonoscopy period. We have also added the 10-year cumulative incidence rate of metachronous multiple SNs in the Results section (page 8, lines 185 and 187).

The 5-year and 10-year cumulative incidence rate of metachronous multiple SNs were significantly higher in patients with synchronous multiple SNs than in those without (61% and 82% versus [vs.] 42% and 51%).

2. Patients with UCANs were excluded from the study, but how many of them had both UCANs and SNs? Also, among patients with SNs, were cases of UCANs that occurred during follow-up omitted from this study?

-> Thank you for your pertinent question. We have added the following text to the Methods section to better explain these aspects (page 4, lines 68–71):

No patient had concurrent UCAN at the time of initial SN detection. However, one patient developed UCANs during the follow-up period after the initial SN diagnosis. Although this patient and the SNs that occurred in this patient were included, the UCANs that occurred in this patient were excluded from this study.

3. The authors used immunohistochemical evaluation of Ki67 and p53 expressions to distinguish between UCANs and SNs. This is a good method. However, it can be difficult to distinguish between UC-associated carcinoma (UCAC) and sporadic cancers. How did the authors make these distinctions clearly?

-> Thank you for raising this pertinent question. We have added the following two sentences to the Methods section (page 5, lines 104–105) and the Results section (page 7, lines 173–175), respectively, to explain these aspects:

The lesions with endoscopically indistinct borders or with dysplasias in the surrounding mucosa were considered UCANs and excluded from this study. (Methods section, page 5, lines 104–105)

All sporadic carcinomas had adenoma components and were diagnosed as sporadic based on the expression patterns of Ki67 and p53 in the adenoma component. (Results section, page 7, lines 173–175)

Minor comments

1. The possibility that treatment for ulcerative colitis, such as steroids or molecularly targeted drugs, may influence the development or growth of colorectal tumours cannot be ruled out. Therefore, the patient's medication or treatment history should be included in Table 1.

-> Thank you for your pertinent suggestion. We have added the use of aminosalicylates, azathioprine, corticosteroids, tacrolimus, anti-TNF- α agents, and integrin inhibitors as the treatment history for patients with UC in Table 1.

2. In Table 1, the mean UC duration (years) is 09.9, is this a mistake of 9.9?

-> Thank you for pointing this out. We have corrected the mean UC duration (years) in Table 1 from “09.9” to “9.9”.

Table 1 Clinical features of the enrolled patients (n=59)

Variable	
Age (years, mean \pm SD ^c)	58.8 \pm 13.7
Sex ^a	
Male	38 (64.4)
Female	21 (35.6)
UC duration (years)	
Mean \pm SD	9.9 \pm 10.6
Median [range]	7 [0–43]
Type of UC	
Total colitis	28 (47.5)
Left-sided colitis	21 (35.6)
Proctitis	10 (16.9)
Clinical course of UC	
Relapse-remitting type	29 (49.2)
Chronic continuous type	14 (23.7)
First attack type	16 (27.1)
Synchronous multiple SNs at initial colonoscopy	14 (23.7)
Metachronous multiple SNs after initial colonoscopy	24 (40.7)
Treatment history for UC ^b	
Aminosalicylates	54 (91.5)
Azathioprine	11 (18.6)
Corticosteroids	14 (23.7)
Tacrolimus	1 (1.7)
Anti-TNF- α agents	5 (8.5)
Integrin inhibitor	1 (1.7)

^a Data are presented as number (%) unless otherwise indicated.

^b There is some overlap in the treatment history of UC.

^c SD: standard deviation, UC: ulcerative colitis, SN: sporadic neoplasia, TNF: tumor necrosis factor

Table 2 Clinicopathological features and endoscopic findings of the SNs^c (n=141)

Variable	
Location ^a	
Cecum	17 (12.1)
Ascending colon	37 (26.2)
Transverse colon	32 (22.7)
Descending colon	6 (4.3)
Sigmoid colon	38 (26.9)
Rectum	11 (7.8)
Background mucosa	
Outside the affected mucosa	100 (70.9)
Within the affected mucosa	41 (29.1)
Tumor size (mm)	
Mean \pm SD	5.8 \pm 6.6
Median [range]	4 [2–50]
Color	
Reddish	30 (21.3)
Normal	111 (78.7)
Gross type	
Protruded	103 (73.1)
Superficial	38 (26.9)
Pit pattern	
III _L	122 (86.5)
IV	3 (2.1)
VI	15 (10.7)
VN	1 (0.7)
Histology	
Adenoma	129 (91.5)
Tis carcinoma	5 (3.5)
T1a carcinoma (SM invasion depth <1000 μ m)	2 (1.5)
T1b carcinoma (SM invasion depth \geq 1000 μ m)	5 (3.5)
Treatment	
Surgical resection ^b	6 (4.3)
Endoscopic resection	135 (95.7)

^a Data are presented as number (%) unless otherwise indicated.

^b Partial colon resection

^c SN: sporadic neoplasia, SM: submucosal, SD: standard deviation

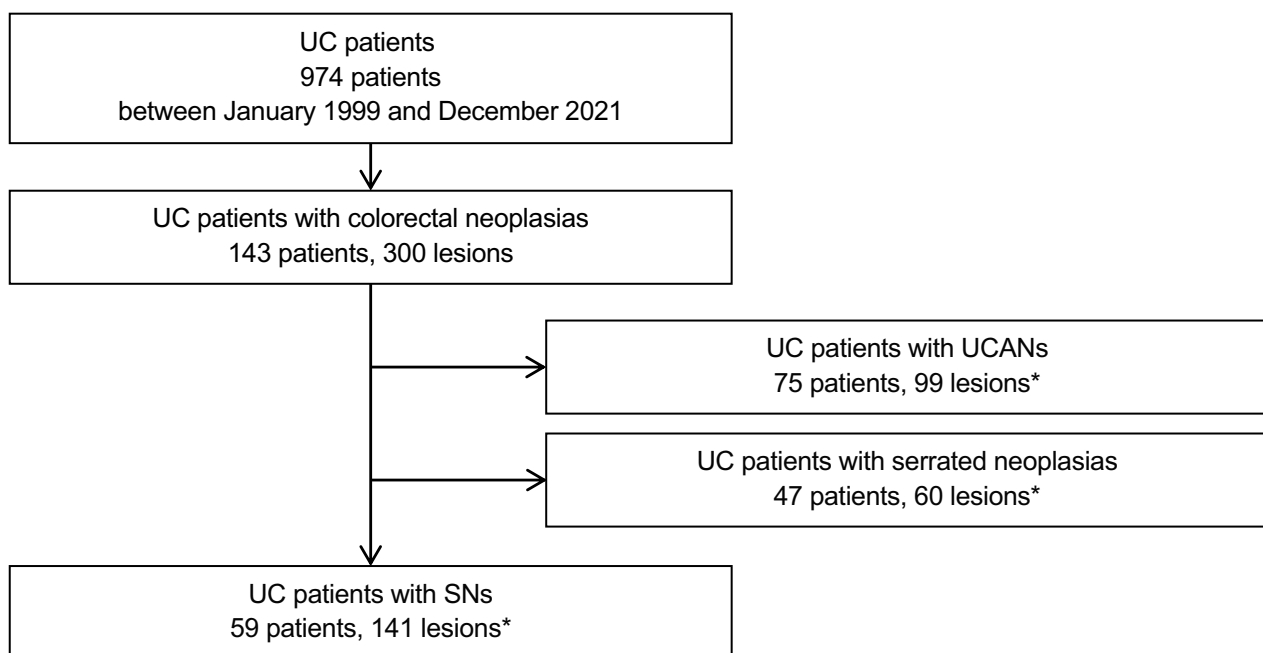
Table 3 Clinicopathological features of 12 sporadic carcinomas in 11 patients

No.	Sex	Age, years	UC ^c duration, months	Type of UC	Clinical course type of UC	Location	Within or outside the affected area	Size, mm	Color	Gross type	Depth	Resection method	Synchronous lesions	Metachronous lesions
1	M	85	516	left-sided colitis	chronic continuous	A/C	outside	20	reddish	protruded	T1b	partial resection	-	-
2	F	72	180	total colitis	relapse-remitting	R	within	5	reddish	superficial	Tis	EMR	-	+
3 ^a	M	73	2	total colitis	first attack	R	within	10	reddish	protruded	Tis	EMR	+	-
4 ^a	M	73	2	total colitis	first attack	S/C	within	15	reddish	protruded	T1b	partial resection	+	-
5	F	72	48	total colitis	chronic continuous	A/C	within	25	reddish	protruded	Tis	ESD	-	-
6	M	57	60	total colitis	chronic continuous	D/C	outside	20	reddish	protruded	Tis	ESD	-	-
7	M	63	5	left-sided colitis	first attack	S/C	within	30	reddish	superficial	T1a	ESD	+	+
8	F	88	240	left-sided colitis	relapse-remitting	A/C	outside	10	reddish	protruded	T1b	partial resection	-	-
9 ^b	M	71	24	total colitis	first attack	A/C	within	40	normal	superficial	Tis	ESD	+	+
10	F	74	120	total colitis	relapse-remitting	A/C	outside	12	reddish	protruded	T1b	partial resection	-	-
11	M	58	1	left-sided colitis	relapse-remitting	A/C	outside	50	normal	superficial	T1b	partial resection	-	-
12	M	52	1	proctitis	relapse-remitting	S/C	outside	6	reddish	protruded	T1a	EMR	+	+

^a Nos. 3 and 4 are different lesions in the same patient.

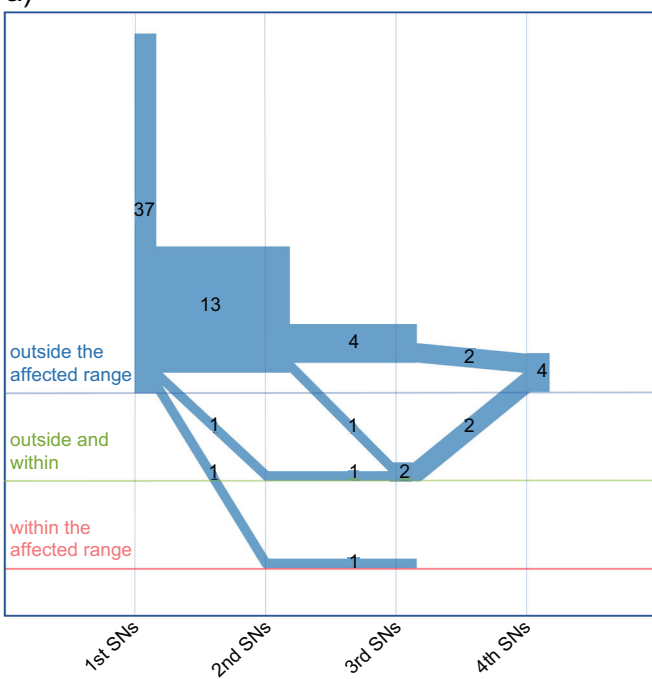
^b Only no. 9 included metachronous adenomas before the carcinoma occurred.

^c UC: ulcerative colitis, M: male, F: female, A/C: ascending colon, D/C: descending colon, S/C: sigmoid colon, R: rectum, EMR: endoscopic mucosal resection, ESD: endoscopic submucosal dissection



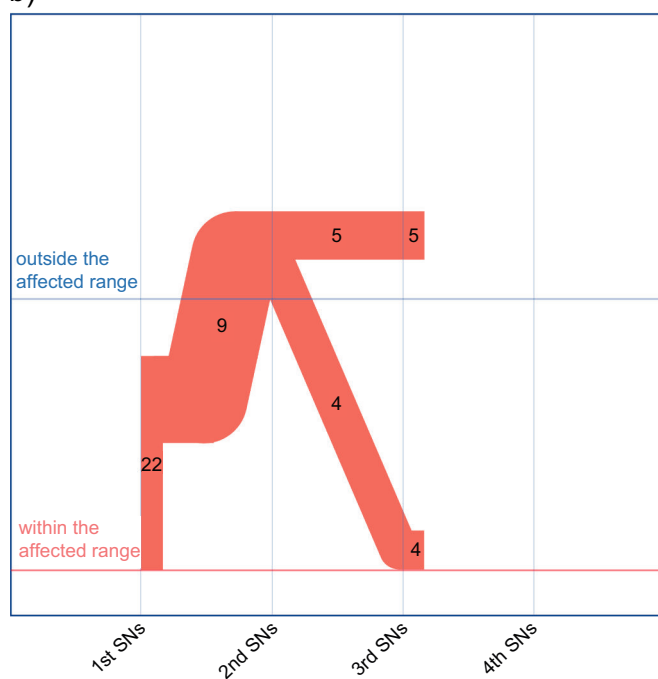
* There is some overlap among the groups.

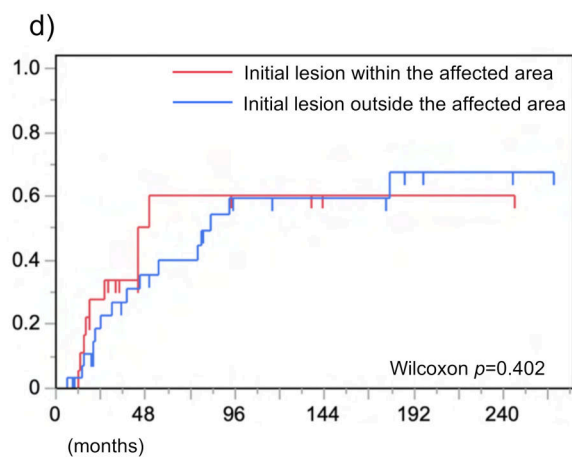
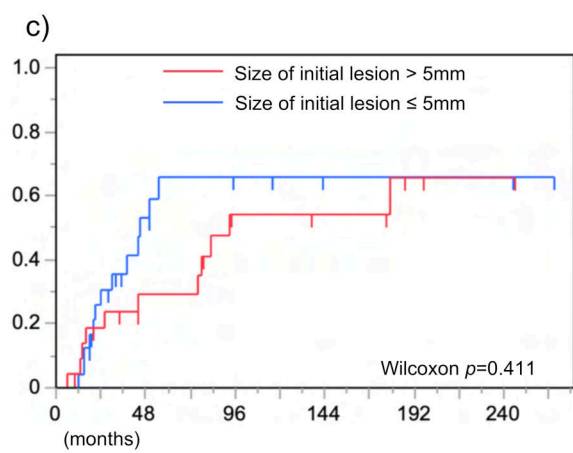
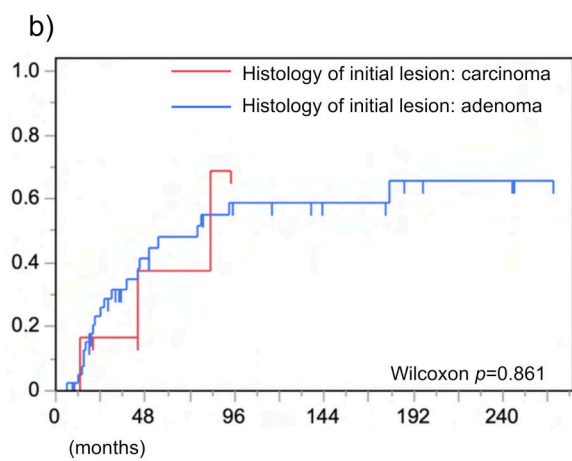
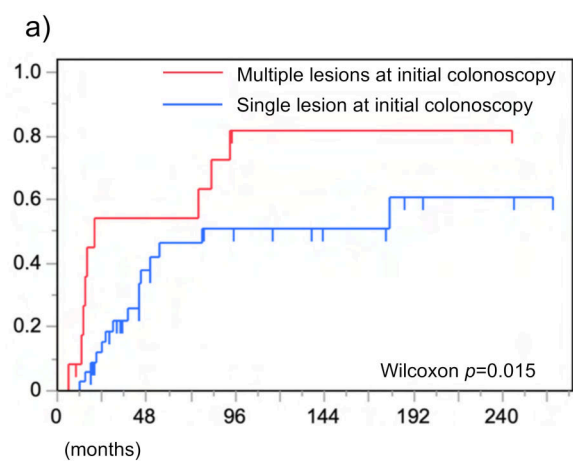
a)



SN: sporadic neoplasia

b)





SN: sporadic neoplasia

January 18, 2024

Volker Ellenrieder and Takuji Gotoda
Editors-in-Chief
Digestion

Dear Editor:

We wish to re-submit the manuscript titled “**Characteristics and prognosis of sporadic neoplasias detected in patients with ulcerative colitis.**” The manuscript ID is DIG-2023-10-5.

We thank you and the reviewers for your thoughtful suggestions and insights. The manuscript has benefited from these insightful suggestions. I look forward to working with you and the reviewers to move this manuscript closer to publication in the *Digestion*.

The manuscript has been rechecked and the necessary changes have been made in accordance with the reviewers’ suggestions. The responses to all comments have been prepared and attached herewith.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,
Ken Yamashita
Department of Gastroenterology, Hiroshima University Hospital
1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan
Telephone: +81 82 257 5193
Fax: +81 82 257 5194
Email: kenయా5@hiroshima-u.ac.jp