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ORIGINAL ARTICLE—ALIMENTARY TRACT

Clinical features and oncological outcomes of intestinal cancers associated with ulcerative colitis and Crohn's disease

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Abstract

Background Patients with longstanding inflammatory bowel disease are at high risk of developing intestinal cancers. In this study, we aimed to elucidate the differences between intestinal cancers associated with ulcerative colitis and Crohn's disease.

Methods Intestinal cancers in ulcerative colitis and Crohn's disease patients treated between 1983 and 2020 at 43 Japanese institutions were retrospectively analyzed..

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Results A total of 1505 intestinal cancers in 1189 ulcerative colitis and 316 Crohn's disease patients were studied. Almost all of ulcerative colitis-associated cancers (99%) were in the colon and rectum, whereas half of Crohn's disease-associated cancers (44%) were in the anus, with 11% in the small intestine. Ulcerative colitis-associated cancers were diagnosed more frequently by surveillance (67% vs. 25%, $P < 0.0001$) and at earlier stages (stages 0–1, 71% vs. 27%, $P < 0.0001$) compared with Crohn's disease-associated cancers. Colorectal cancers associated with Crohn's disease showed a significantly worse 5-year overall survival rate than those associated with ulcerative colitis (stage 2, 76% vs. 89%, $P = 0.01$, stage 3, 18% vs. 68%, $P = 0.0009$, and stage 4, 0% vs. 13%, $P = 0.04$). Surveillance correlated with earlier diagnoses for ulcerative colitis- and Crohn's disease-associated intestinal cancers, whereas shorter intervals between endoscopic examinations correlated with an earlier cancer diagnosis in ulcerative colitis patients but not in Crohn's disease patients.

Conclusions The clinical and oncological features of ulcerative colitis- and Crohn's disease-associated cancers were very different. Crohn's disease-associated cancers were diagnosed at more advanced stages and were detected less frequently by surveillance. Additionally, they showed a significantly poorer prognosis.

Keywords Crohn's disease · Intestinal cancers · Ulcerative colitis

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Abbreviations

JSCCR	Japanese Society for Cancer of the Colon and Rectum
ACG	American College of Gastroenterology
IBD	Inflammatory bowel disease
UC	Ulcerative colitis
CD	Chrohn's disease

Introduction

The number of patients with inflammatory bowel disease (IBD) is increasing [1], and patients with longstanding IBD are known to be at a higher risk for developing intestinal cancers than the general population [2, 3]. Recent improvements in medical therapy for IBD are believed to have decreased the need for surgical treatment, thus increasing the number of patients with longstanding IBD maintained on medical therapy and the number of surgeries indicated for cancer or dysplasia [4]. The importance of cancer surveillance is increasingly being recognized in longstanding IBD patients [5–10]. Unfortunately, owing to insufficient data, it has been difficult to define the optimal surveillance protocol for IBD and establish standard a time period between colonoscopic surveillance [8–12]. Cancer surveillance in CD patients is more complex. The risk of small bowel malignancies is reportedly to be significantly higher in CD patients than in the general population [13, 14], and surveillance for small bowel cancers remains difficult and controversial in these patients [15].

Patient survival after the development of IBD-associated intestinal cancers has been reported to be poor, especially for cancers presenting at more advanced stages [16, 17]. Furthermore, survival rates for patients having colorectal cancers associated with CD are much lower than for patients with sporadic cancers [18, 19], and small bowel cancers associated with CD have an extremely poor prognosis [15]. Additionally, there are limited data regarding differences between the oncological outcomes of UC-associated versus CD-associated cancers, although these two types of malignancies have different clinical features [20].

Thus in this study, we aimed to clarify the differences in the clinical and pathological characteristics, diagnostic procedures, and oncological outcomes of UC- and CD-associated intestinal cancers using a large multicenter cohort to understand how these IBD-associated cancers can be diagnosed and treated more efficiently to improve oncological outcomes in IBD patients.

Methods

Data registration

Patient data were collected from 43 institutions, including surgery and gastroenterology departments, in the Japanese Society for Cancer of the Colon and Rectum (JSCCR). Ulcerative colitis and CD patients who had been diagnosed with intestinal cancers from 1983 to 2020 were included in this study. The patients' data were retrospectively collected from medical records at each institution and then sent to the Department of Surgical Oncology at the University of Tokyo for further analyses. We collected baseline information on patients' characteristics, diagnostic procedures, treatment details, histopathological findings, and long-term oncological outcomes. These data were then compared between UC- and CD-associated intestinal cancers. In addition, information about whether the cancers were sporadic or were associated with IBD was also collected based on pathological diagnoses at each institution.

Ethics

This study was approved by the Ethics Committee of the University of Tokyo [2019220NI-(2)], the ethics committees of each institution if necessary, and the Ethics Committee of JSCCR, and they decided that the requirement for written informed consent from patients for participation in this study was waived due to the retrospective study design.

Statistical analysis

Statistical analyses were performed using JMP Pro 15 (SAS Institute Inc, Cary, NC, USA). Comparisons of patient and clinical characteristics between groups were evaluated using the Student's *t* test for continuous variables and Pearson's chi-squared test or Fisher's exact test for categorical variables, as appropriate.

Survival analysis was performed using the Kaplan–Meier method and was compared using the log-rank test, and a multivariate analysis using the Cox proportional hazards model was also performed. When analyzing the oncological outcomes of the patients with multiple lesions, the most advanced lesion was analyzed. We compared overall survival (OS) of colorectal cancer between UC and CD patients, and then showed OS of small intestinal and anal canal cancers in CD patients separately, because small intestinal and anal cancers had a very different prognosis to colorectal cancers.

Due to the retrospective registration of the patient data, there were missing data in the data set. Since the percentages of the missing data for most of the variables were less than 10%, we excluded the missing data for each analysis in this study. Furthermore, to examine the validity of the analysis, we added sensitivity analyses. We applied hot-deck imputation which handles missing data in which each missing value is replaced with a random sample of observed variables from a "similar" unit regarding the following eight variables (age at IBD diagnosis, sex, diagnostic procedure, location of cancer lesions, synchronous multiple lesions, histologic type, pathological stage, and status of overall survival).

Results

Patient backgrounds

A total of 1505 IBD patients with intestinal cancers were analyzed, including 1189 with UC and 316 with CD. The median follow-up period after the treatment (surgical or endoscipic resection cases) or the diagnosis of cancer (no resection cases) was 46 (range 0–388) months.

The median ages at IBD diagnosis and at subsequent cancer diagnosis were significantly younger in CD patients, and the duration of IBD at cancer diagnosis was significantly longer in CD patients (Table 1).

Cancer information

The anatomical distributions of cancer lesions were quite different between the UC and CD patients (Table 1; Figure S1). Nearly half of CD-associated intestinal cancers were located in the anus (44%), with 11% located in the small intestine; the majority of which were in the ileum. In contrast, 99% of the cancers in UC patients were located in the colon and rectum. And anal cancer was rare (1%) and no small intestinal cancer was reported in UC patients.

In the UC patients, the majority of cancers were histologically classified as being well- or moderately differentiated adenocarcinomas (73%). In contrast, 39% of the CD-associated cancers were histologically classified as mucinous carcinomas. In terms of the suspected pathogenesis of cancers, the majority were categorized as colitis-associated cancers in UC and CD patients. Dysplasia and synchronous multiple lesions were identified more frequently in the UC patients, while the pathological stage was more advanced in CD patients (Table 1).

Treatment

The majority of patients were treated with surgical resection for UC- and CD-associated cancers. Endoscopic

Table 1 Clinical and pathological features and treatment details of the study population

	UC (n = 1189)	CD (n = 316)	P value
Age at IBD diagnosis[a]	33 (7–83)	25 (10–71)	< 0.0001
Age at cancer/dysplasia diagnosis[a]	52 (19–89)	46 (21–82)	< 0.0001
Duration of IBD (month)[a]	192 (0–648)	240 (0–624)	< 0.0001
Sex			
Male	738 (62%)	212 (67%)	0.1308
Diagnostic procedure			
Surveillance	793 (67%)	79 (25%)	< 0.0001
Workup for symptom	303 (26%)	175 (56%)	
Other	83 (7%)	60 (19%)	
Location of cancer lesions			
Small intestine	0	32 (11%)	< 0.0001
Colon and rectum	1146 (99%)	129 (45%)	
Anus	11 (1%)	128 (44%)	
Suspected pathogenesis			
Colitc	931 (83%)	177 (62%)	< 0.0001
Sporadic	107 (10%)	16 (6%)	
Undetermined	85 (8%)	91 (13%)	
With dysplasia	559 (49%)	37 (13%)	< 0.0001
Synchronous multiple lesions	286 (25%)	31 (14%)	0.0004
Histologic type			
wel	617 (56%)	82 (28%)	< 0.0001
mod	192 (17%)	44 (15%)	
por	72 (7%)	15 (5%)	
muc	75 (7%)	114 (39%)	
sig	30 (3%)	17 (6%)	
scc	4 (0.4%)	8 (3%)	
other	114 (10%)	14 (5%)	
Pathological stage			
0	338 (32%)	27 (10%)	< 0.0001
1	307 (29%)	43 (17%)	
2	184 (17%)	97 (37%)	
3	184 (17%)	58 (22%)	
4	48 (5%)	36 (14%)	
Treatment procedure			
Surgical resection	1113 (93%)	303 (96%)	< 0.0001
Endoscopic resection	71 (6%)	2 (0.6%)	
No resection	5 (0.4%)	11 (4%)	
R0 resection	1043 (95%)	210 (74%)	< 0.0001

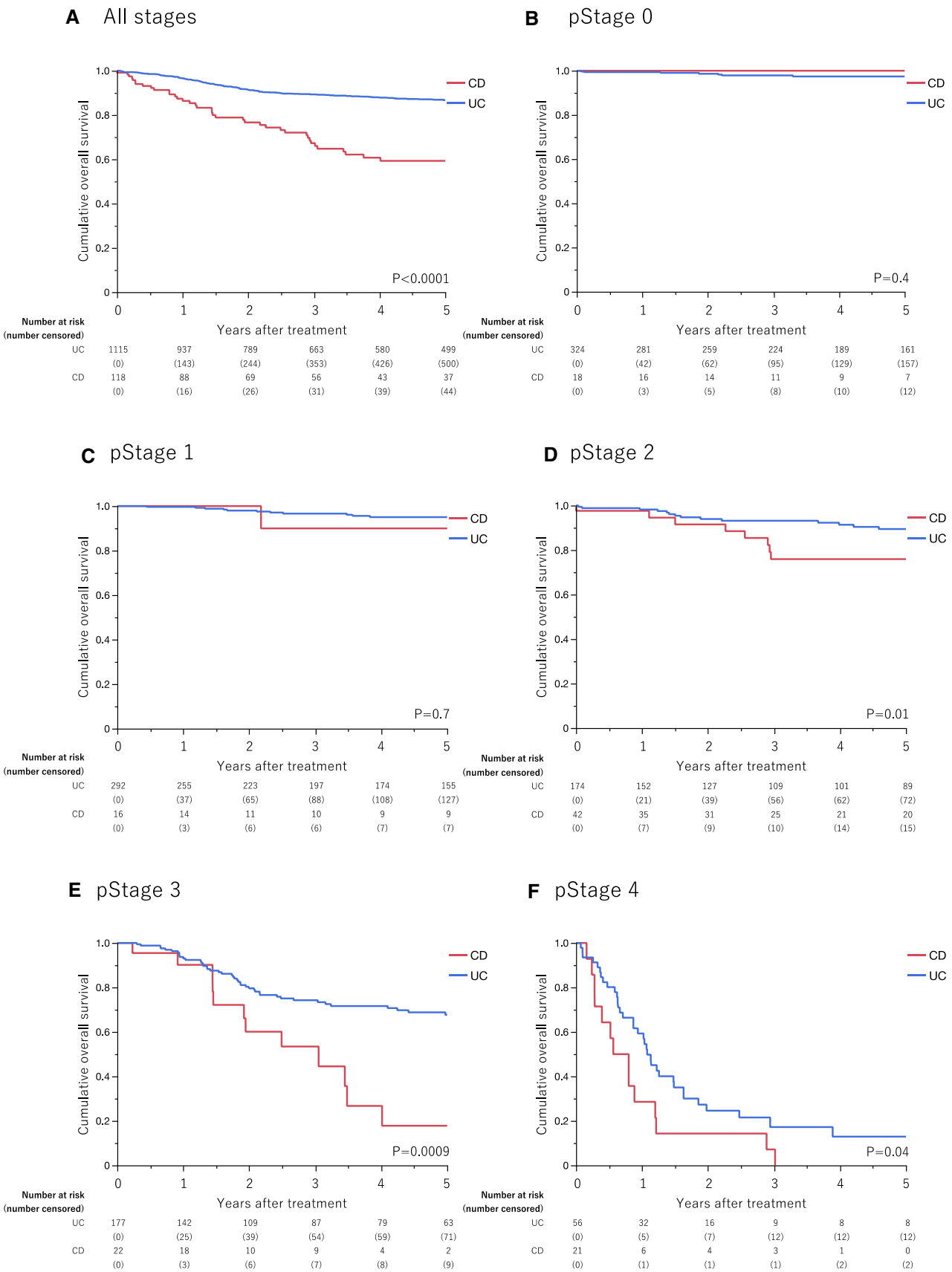
[a]Data are presented as medians (ranges)

UC, ulcerative colitis; *CD,* Crohn's disease; *IBD,* inflammatory bowel disease; *wel,* well-differentiated adenocarcinoma; *mod,* moderately differentiated adenocarcinoma; *muc,* mucinous adenocarcinoma; *sig,* signet-ring cell carcinoma; *scc,* squamous cell carcinoma; *R0, resection* resection without residual disease

resections were performed more frequently in UC patients, and the cancer lesions were not resected more frequently in the CD patients, mainly due to the more advanced stage of the disease. Resection of cancers was more frequently curative (R0) in UC patients (Table 1).

Prognosis

Overall survival (OS) of cancers of the colon and rectum was compared between UC and CD patients (Fig. 1). The CD patients showed a significantly worse 5-year OS rate than the UC patients (59% vs. 87%, respectively,


A All stages
Cumulative overall survival
1.0
0.8
0.6
0.4
0.2
0
CD
UC
P<0.0001
0 1 2 3 4 5
Years after treatment
Number at risk
(number censored)
UC 1115 937 789 663 580 499
(0) (143) (244) (353) (426) (500)
CD 118 88 69 56 43 37
(0) (16) (26) (31) (39) (44)
B pStage 0
Cumulative overall survival
CD
UC
P=0.4
Years after treatment
Number at risk
(number censored)
UC 324 281 259 224 189 161
(0) (42) (62) (95) (129) (157)
CD 18 16 14 11 9 7
(0) (3) (5) (8) (10) (12)
C pStage 1
Cumulative overall survival
CD
UC
P=0.7
Years after treatment
Number at risk
(number censored)
UC 292 255 223 197 174 155
(0) (37) (65) (88) (108) (127)
CD 16 14 11 10 9 9
(0) (3) (6) (6) (7) (7)
D pStage 2
Cumulative overall survival
CD
UC
P=0.01
Years after treatment
Number at risk
(number censored)
UC 174 152 127 109 101 89
(0) (21) (39) (56) (62) (72)
CD 42 35 31 25 21 20
(0) (7) (9) (10) (14) (15)
E pStage 3
Cumulative overall survival
CD
UC
P=0.0009
Years after treatment
Number at risk
(number censored)
UC 177 142 109 87 79 63
(0) (25) (39) (54) (59) (71)
CD 22 18 10 9 4 2
(0) (3) (6) (7) (8) (9)
F pStage 4
Cumulative overall survival
CD
UC
P=0.04
Years after treatment
Number at risk
(number censored)
UC 56 32 16 9 8 8
(0) (5) (7) (12) (12) (12)
CD 21 6 4 3 1 0
(0) (1) (1) (1) (2) (2)

◀**Fig. 1** Overall survival (colon and rectal cancer). The overall survival of patients with ulcerative colitis (UC)-associated cancers was better than the overall survival of patients with Crohn's disease (CD)-associated cancers in the whole subgroup (**A**) and in patients with stage 2–4 cancers (**D–F**)

$P < 0.0001$, Fig. 1A). When stratified by pathological staging, OS of stage 0–1 colorectal cancers was good and not different between UC and CD patients (Fig. 1B, C); however, the CD patients with stage 2–4 cancers showed a significantly worse OS than the UC patients (Fig. 1D–F). OS of cancers of the small intestine and the anus in CD patients stratified by pathological staging is shown in Fig. 2A, B. A multivariate analysis for OS revealed that CD, in addition to the advanced pathological staging and noncurative resection, was independently associated with a poor OS (Table 2).

Recurrence of all intestinal cancer was observed in 129 UC patients and 101 CD patients ($P < 0.0001$). A breakdown of recurrence sites is shown in Figure S2. The most frequent location of recurrence was peritoneal in UC patients and locoregional in CD patients.

Surveillance and diagnosis

The majority of cancers were diagnosed by surveillance in UC patients. In contrast, only 25% of the CD-associated cancers were diagnosed by surveillance, with more than half of cancers diagnosed as a result of workups for symptoms in the CD patients (Table 1).

For UC-associated cancers, most surveillance was performed by endoscopic examination (99%). Among the surveillance modalities for CD cancers, endoscopic examination was the most frequent (78%), followed by trans-anal biopsy in 13% of cases.

As shown in Fig. 3, cancer detection via surveillance was correlated with a cancer diagnosis at a significantly earlier stage than for the symptomatic cases for UC and CD patients. However, it is notable that stage 2–4 cancers comprised a significant proportion of the cancers detected by surveillance, including 27% and 58% in UC and CD patients, respectively.

As endoscopic examinations represented the most common modality for surveillance, we examined the correlations between the interval between endoscopic examinations and cancer staging with a shorter interval, significantly correlated with a diagnosis at an earlier stage in UC patients but not in the CD patients (Fig. 4). Again, it is notable that even the shortest endoscopy interval (0–1 year) could not eliminate a diagnosis of stage 2–4 cancer in 29% and 63% of the UC- and CD-associated cancers, respectively. Cancers found by surveillance showed a significantly better OS rate than the symptomatic cases in the UC and CD patients (Fig. 5).

Sensitivity analysis

The numbers and percentages of missing patient data are provided in Table S1. Although most variables had missing data less than 10%, for two variables (multiple lesions and pathological stage), the percentages of missing data were relatively high (32% for multiple resions and 16% for pathological stage) in CD patients. The number of patients who have missing data regarding one of eight variables (age at IBD diagnosis, sex, diagnostic procedure, location

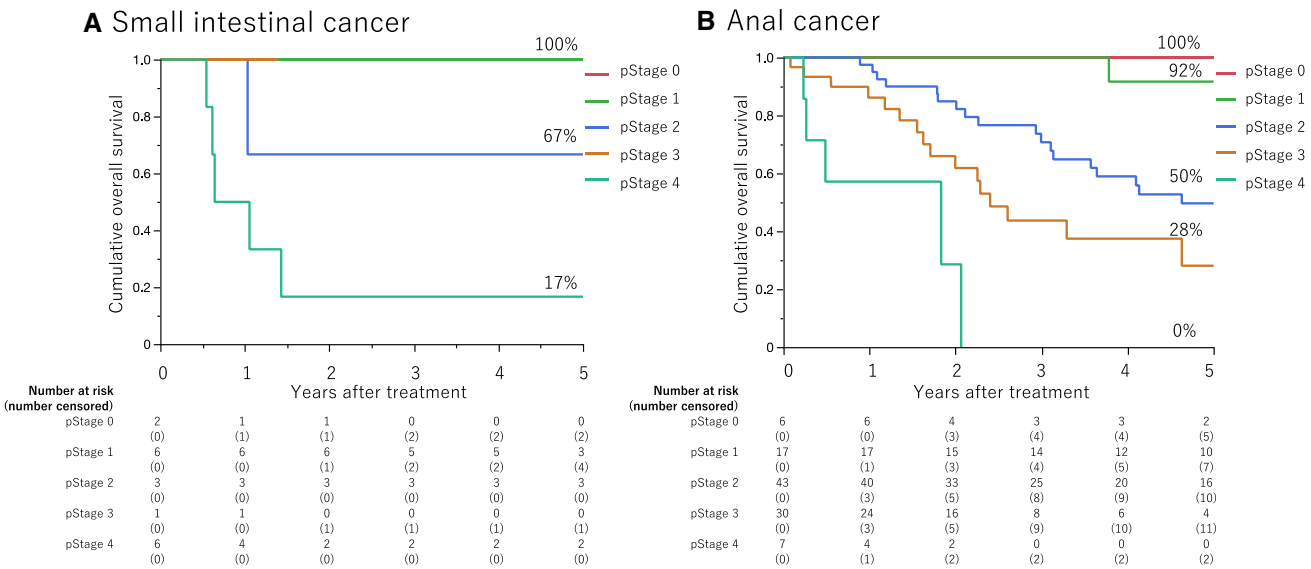


Fig. 2 Overall survival (small intestinal cancer and anal cancer in CD patients). The overall survival of patients with small intestinal cancers (**A**) and anal cancers (**B**) associated with Crohn's disease (CD) stratified by pathological cancer stage

Table 2 Multivariate analysis for overall survival

	Univariate	Multivariate	
	P value	P value	HR (95% CI)
CD/UC	< 0.0001	0.0025	2.36 (1.35–4.14)
Age at IBD diagnosis (> 35)	0.0018	0.146	
Age at cancer/dysplasia diagnosis (> 50)	0.0003	0.4608	
Sex	0.0465	0.1302	
Diagnostic procedure	< 0.0001	0.4075	
Location of cancer lesions	< 0.0001	0.4692	
Suspected pathogenesis	< 0.0001	0.5622	
With dysplasia	< 0.0001	0.1728	
Synchronous multiple lesions	0.1394		
Histologic type	< 0.0001	0.3927	
Pathological stage	< 0.0001	< 0.0001	
0			1
1			1.95 (0.82–4.65)
2			4.36 (1.86–10.20)
3			10.17 (4.46–23.12)
4			37.34 (14.38–96.98)
Treatment procedure	< 0.0001	1	
R0/R1-2 resection	< 0.0001	0.0005	0.41 (0.25–0.68)

CD, Crohn's disease; *UC,* ulcerative colitis; *IBD,* inflammatory bowel disease; *HR,* hazard ratio; *CI,* confidence interval

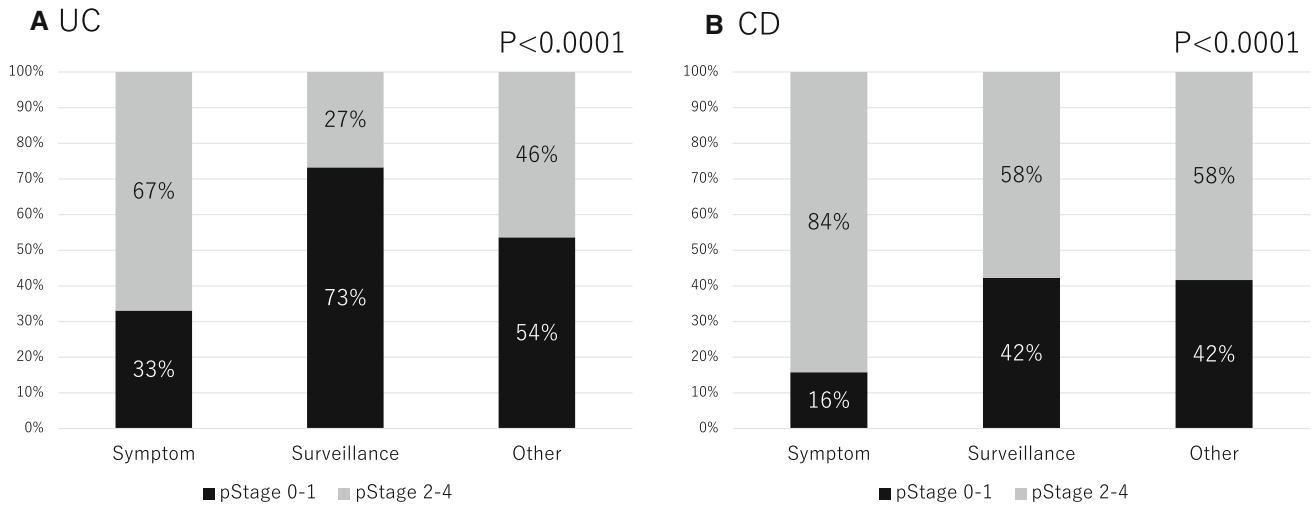


Fig. 3 Cancer stages in surveillance and symptomatic cases. The proportion of early-stage (stage 0–1) cancers was higher in surveillance versus symptomatic cases both for ulcerative colitis (**A**) and Crohn's disease (**B**) patients

of cancer lesions, multiple lesions, histologic type, pathological stage, and status of overall survival) was 337 out of all patients. We applied hot-deck imputation which handles missing data in which each missing value is replaced with a random sample of observed variables from a "similar" unit regarding eight variables. The details of the imputed data set was shown in Table S2, and the results were similar to those in the original Table 1. As shown in Figures S3–S7, similar results were obtained in the sensitivity analyses using this imputed data set for prognosis, surveillance, and diagnosis.

Discussion

The present multicenter study examined the characteristics of IBD-associated intestinal cancers in Japan, demonstrating that the clinical and pathological features, oncological

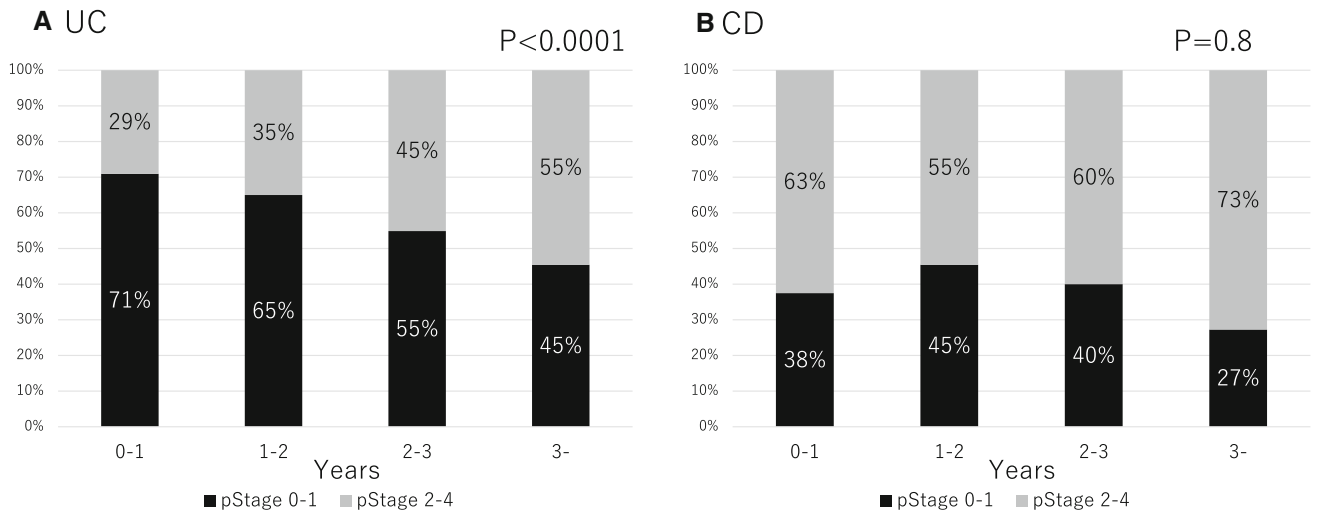


Fig. 4 Interval of endoscopic examinations and cancer stages. In ulcerative colitis patients (**A**) but not in Crohn's disease patients (**B**), a shorter interval between endoscopic examinations was correlated with a cancer diagnosis at an earlier stage (stage 0–1)

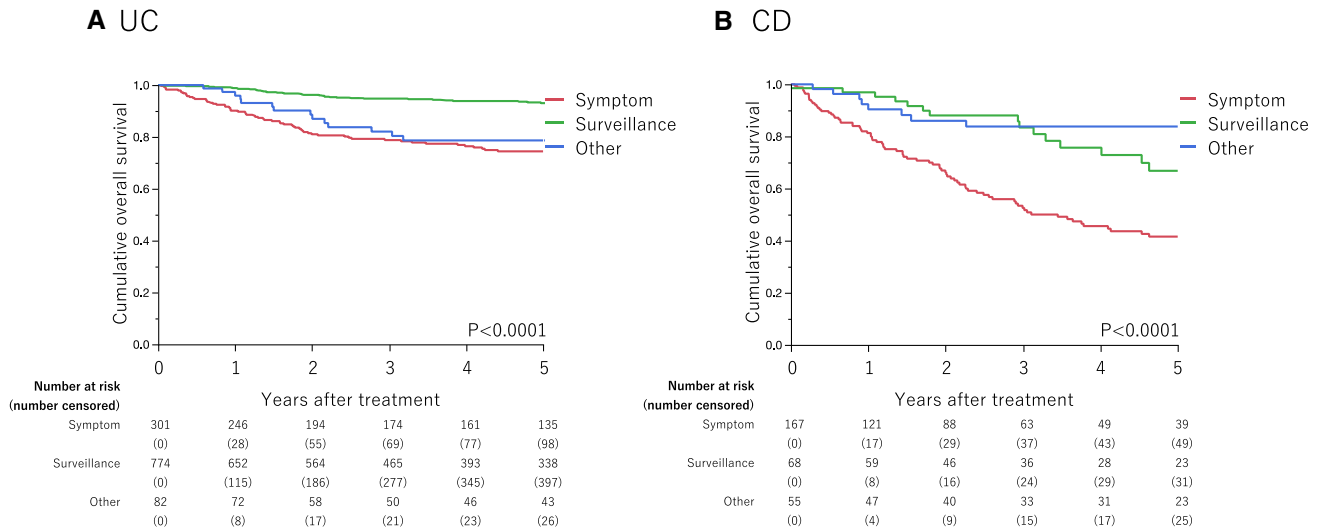


Fig. 5 Overall survival of surveillance and symptomatic cases. Cancers found by surveillance showed a significant better OS rate than symptomatic cases, both in UC (**A**) and CD patients (**B**)

outcomes, and diagnostic procedures were very different between UC and CD patients.

Previous studies have shown that UC- and CD-associated colorectal cancers have a poorer prognosis than cancers in non-IBD patients [16, 19, 21]. In this study, OS rates of patients with UC- and CD-associated intestinal cancers were relatively poor, especially for patients with more advanced diseases. Among cancers of the colon and rectum, the 5-year OS rates of UC- and CD-associated cancers were 68% and 18% for stage 3 disease, respectively, and as low as 13% and 0% for stage 4 disease, respectively. The corresponding OS rates reported in a Japanese multicenter registry were 66.3%–80.1% and 27.6%, respectively [22].

The CD-associated cancers were diagnosed at more advanced stages and showed a worse OS rate than the UC cancers. The poorer prognosis of CD-associated cancers was especially evident when comparing the OS rates of patients with stage 2–4 cancers of the colon and rectum. Mucinous carcinomas and noncurative resections were more common in CD-associated cancer patients, both of which may contribute to the poorer prognosis of CD-associated cancers. However, a multivariate analysis incorporating these factors revealed that CD was independently associated with a poor OS, and this finding suggests that cancers that develop in CD patients may have a more aggressive oncological behavior.

Previous studies have suggested that surveillance can improve the prognosis of IBD-associated cancers by enabling diagnoses at earlier disease stages [23–25]. In accordance with these reports, cancers diagnosed by surveillance in this study were more likely to be detected at earlier stages with a better OS than cancers diagnosed by workups for symptoms in the UC and CD patients. These findings suggest the importance of surveillance for UC and CD patients. The most important related concern, however, was that only 25% of the CD-associated cancers were diagnosed by surveillance, which contrasts considerably with UC-associated cancers, of which nearly 70% were diagnosed by surveillance. One reason for the less frequent surveillance-based diagnosis of CD-associated cancers may be the locations of these lesions, which differed significantly from the UC cancers. In this study, the CD-associated cancers were more likely to be located in the ileum and anus. Previous reports have demonstrated that CD patients have up to 40-fold excess risk of developing small intestinal cancers [13, 14]. Indeed, in this study, more than 10% of intestinal cancers in CD patients were located in the small intestine. Of note, most surveillance in this study was conducted via endoscopic examinations, and it can be more difficult to examine the small intestine than the large intestine endoscopically. Therefore, the introduction of a more feasible surveillance modality for small intestinal cancers in CD patients is necessary. Nearly half of cancers in CD patients were located in the anus, which is a characteristic of CD-associated cancers in Japan [26]. Surveillance for anal cancers requires an inspection of the anus, as well as a trans-anal biopsy under anesthesia in some cases, which can be burdensome for the patient and doctor. Whether CD patients have an increased risk of cancer of the colon remains controversial [13, 19, 27], and, in this study, the proportion of cancers of the colon, from the cecum to the rectosigmoid, was relatively low, accounting for only 20% of the intestinal cancers.

Patient age and the duration of IBD at cancer diagnosis are important characteristics to consider when determining when to start surveillance for cancer. Recent guidelines of the American College of Gastroenterology (ACG) recommend that surveillance colonoscopies start 8 years after UC diagnosis [8]. This recommendation seems reasonable since the median duration of UC was 192 months (16 years) in this study, and patients with a duration of UC of more than 8 years comprised 82% of all the UC-associated cancer patients (Figure S7). However, it was also notable that a non-negligible proportion (18%) of cancers were diagnosed within 8 years of a UC diagnosis, and the duration of UC did not correlate with the cancer stage at diagnosis nor the subsequent OS (data not shown).

The ages at IBD diagnosis and at subsequent cancer diagnosis were significantly lower among the patients with CD; however, the duration of IBD was significantly longer for CD patients than for UC patients. It is not clear whether this longer duration resulted from a longer required time period for cancers to develop from chronic inflammation in the CD patients or resulted merely from less frequent and more demanding surveillance procedures, which could lead to delays in cancer diagnosis and is suggested by the more advanced stage of cancer in the CD patients. Further investigation of this question is certainly necessary.

In the UC-associated cancer patients, a shorter interval between endoscopic examinations was associated with an earlier stage of cancer at diagnosis, which suggests the importance of regular endoscopic surveillance. However, when that interval exceeded 3 years, more than half of cancers were diagnosed at more advanced stages. The ACG guidelines recommend that surveillance colonoscopies should be performed at 1–3-year intervals [8], and this study's observations support that recommendation. However, the optimal interval should be determined in accordance with a patient's risk for cancer incidence, and further studies are necessary to understand this relationship.

The guidelines of the Crohn's and Colitis Foundation of America recommend a similar surveillance colonoscopy program for CD patients; however, data supporting regular colonoscopic surveillance of CD patients are more limited than for UC patients. In this study, a shorter interval between endoscopic examinations did not correlate with an earlier diagnosis of cancer in CD patients, which underscores the difficulty and reduced efficacy of regular endoscopic surveillance in CD-associated cancers.

It is notable that a significant proportion of cancers were diagnosed at stages 2–4 within an interval of less than 1 year from the previous endoscopic examination, even in UC cancer patients. This finding may partially be due to the less obscure macroscopic appearance of the IBD-associated colorectal cancers, which are typically flat, non-protruding lesions with unclear margins versus sporadic colorectal cancers. For this reason, random biopsies performed during endoscopic surveillance examination are less likely to miss obscure neoplastic lesions in the IBD. However, recent randomized studies have shown the safety and cost-effectiveness of targeted versus random biopsies [5, 28]. Therefore, the optimal surveillance method for these patients remains to be elucidated.

This study had some limitations. The first was the retrospective nature of the analyses, and there is a possibility that some cases were missing in the database of each institution, and this recall or selection bias might have influenced the results of this study. Nevertheless, this study precisely examined and reported a relatively large number of intestinal cancers in UC and CD patients, and patient data were collected from a wide variety of centers, including those not specializing in IBD treatment, which is

a strength of this study. There were some missing data due to the retrospective registration of data for the patients treated in a relatively long period of time. However, percentages of the missing data for most of the variables were less than 10%, and the sensitivity analyses using the imputed data set revealed similar results. The second limitation was that the diagnoses of IBD and associated cancers were made at each institution and not centralized. Thus, these diagnoses may not have been uniformly performed. In addition, UC and CD are sometimes difficult to differentially diagnose from one another. The third limitation was that all the data were obtained from Japanese institutions, and, therefore, the results may not be generalizable to other countries. Finally, the data described in the present study include cases during the long study period, for which the treatment patterns and oncological outcomes may significantly vary depending on the time of diagnosis, and therefore further analysis is warranted.

Conclusion

This study showed that the clinical and pathological features of intestinal cancers in UC and CD patients were very different. CD-associated cancers were diagnosed at more advanced stages and had a poorer prognosis than UC-associated cancers. In general, regular surveillance was correlated with an earlier cancer diagnosis and a better prognosis. However, cancer diagnoses at more advanced stages could not be satisfactorily eliminated, even by intensive surveillance. Surveillance seems more complex and difficult in CD patients than in UC patients due to the more frequent distributions of these cancers in the rectum, anus, and small intestine.

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Authors contribution SI is the chief investigator of this study group and the corresponding author; contributed to the design of the work, the analysis, and interpretation of data for the work; and revised the manuscript critically for important intellectual content. TN is the first author and contributed to the acquisition of data for the work, and drafted the work. KS and YA contributed to the conception of the work, and revised the work critically for important intellectual content. MU, HI, KO, KF, ST, HO, HN, KW, MI, KO, YT, TM, MN, KY, TW, YS, HK, KT, KH, YK, JO, KD, FK, HU, TY, TH, AM, and JA contributed to the acquisition of the data for the work, and revised the work critically for important intellectual content. KW, KH, JO, FK, HU, and AM contributed to the analysis of the data for the work, and revised the work critically for important intellectual content. HI, KF, ST, HO, KW, MI, YT, TM, MN, TW, KT, KH, YK, JO, KD, and KO contributed to the interpretation of the data for the work, and revised the work critically for important intellectual content. All the authors approved the final version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The funding source had no role in study design, data collection, data analysis and interpretation, preparation of the manuscript, or decision to publish.

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Data accessibility statement The data underlying this article will be shared after all the analyses are completed on reasonable request to the corresponding author.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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