

Impact of Crohn's Disease on the Survival of Patients with Small-Bowel Adenocarcinoma in Korea: A Bicenter Cohort Study

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Background/Aims: Owing to the low prevalence of small-bowel adenocarcinoma (SBA), data on the impact of Crohn's disease (CD) on the survival of patients with SBA are lacking. Therefore, we investigated this issue in this study.

Methods: In this bicenter cohort study, patients with histologically confirmed SBA were retrospectively enrolled and classified into two groups: sporadic SBA and CD-associated SBA. Patients with duodenal SBA were excluded. Overall survival, disease-free survival, and factors associated with survival were analyzed.

Results: Of 128 patients with SBA, 115 had sporadic SBA and 13 had CD-associated SBA. Ileal involvement and poorly differentiated tumors were more common in the CD-associated SBA group than in the sporadic SBA group (ileal involvement, 53.8% vs 22.6%; poor differentiation, 46.2% vs 14.8%; both $p < 0.05$). In survival analysis, overall survival showed no statistical difference between the sporadic SBA and CD-associated SBA groups ($p = 0.370$). However, when stratified by stage, the adjusted overall survival of the CD-associated SBA group was lower in patients with an advanced disease stage ($p = 0.029$). Disease-free survival showed the same tendency, albeit without clinical significance ($p = 0.097$). CD (hazard ratio [HR], 2.308; $p = 0.047$), older age (≥ 65 yr) at SBA diagnosis (HR, 2.766; $p = 0.001$), and stage III/IV disease (HR, 3.151; $p < 0.001$) were factors associated with mortality.

Conclusions: The overall survival of patients with CD-associated SBA did not differ from that of patients with sporadic SBA. However, as CD is an independent risk factor for mortality, vigilant surveillance in high-risk patients may be crucial. (*Gut Liver* 2023;17:581-590)

Key Words: Small-bowel adenocarcinoma; Crohn disease; Overall survival; Disease-free survival

INTRODUCTION

With accumulating evidence on a rapid increase in the incidence and prevalence of inflammatory bowel disease in Asian countries,¹ concerns about not only the optimal treatment of inflammatory bowel disease but also inflammatory bowel disease-related consequences, such as an increased risk of carcinomas of the gastrointestinal tract, have arisen.² Gastrointestinal cancer presumably results from chronic inflammation of involved bowel segments and is partly affected by use of immunomodulators or

biologic agents.^{3,4} Small-bowel (SB) cancer accounts for 1% to 5% of all gastrointestinal malignancies, with adenocarcinoma being one of the most common histologic subtypes. Although the absolute risk is low, with a prevalence ranging from 1.6% to 9%,⁵⁻⁸ SB adenocarcinoma (SBA) is a major concern, with a low 5-year overall survival (OS) rate of 30% in patients with Crohn's disease (CD).^{9,10} In particular, patients with CD have a 67-fold higher risk of developing SBA than the general population.^{5,11-18} In a meta-analysis of 20 studies by Laukoetter *et al.*,¹⁸ the relative risk in patients with CD was 18.7 compared to a background

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matched population. In addition, in a French nationwide cohort study, the standardized incidence ratios of SBA among patients with SB CD and those with SB CD for >8 years were 34.9 and 46.0, respectively.¹⁹

In a bi-national population-based cohort study from Sweden and Denmark, patients with CD had a 9-fold higher incidence of SB cancer and a 7-fold higher risk of death from SB cancer than the general population.²⁰ Several studies have reported risk factors associated with the development of SB cancer in patients with CD, including long disease duration, young age at diagnosis, disease localization (distal jejunum and ileum), male sex, phenotype (stricturing and chronic penetrating disease), use of steroids and immunomodulators, SB bypass loops, and other environmental factors.^{2,18,21-29} In addition, a single case-control study by Piton *et al.*³⁰ suggested that SB resection and use of aminosaliculates for >2 years are protective factors against SBA development. Among various risk factors for SBA, inflamed intestinal segments were observed in almost all case series and meta-analyses, and long-standing CD and stricturing disease seemed to have the strongest association with SBA.²

Meanwhile, some previous studies have investigated the association between CD and mortality in patients with SBA. Some studies reported poor survival in patients with CD-associated SBA,^{7,14,31-33} whereas other studies demonstrated no difference in survival between patients with CD-associated SBA and those with sporadic SBA.^{5,6,10} In a recent study by Fields *et al.*⁹ based on a U.S. National Cancer Database Registry, patients with CD-associated SBA had similar OS to those with sporadic SBA, and CD was not an independent risk factor for mortality. These varying results from earlier studies imply the difficulty in defining the effect of CD on SBA, along with the low prevalence of SBA and the difficulty of its diagnosis.

Data on the impact of CD on the survival of patients with SBA remain insufficient, and data from Asian countries are nearly deficient. Therefore, in this study, we aimed to compare the clinical features of CD-associated SBA and sporadic SBA and to investigate the impact of CD on the survival of patients with SBA.

MATERIALS AND METHODS

1. Study population

From January 1998 to November 2021, patients with histologically confirmed SBA were reviewed at two tertiary care hospitals (Asan Medical Center and Seoul National University Hospital) in South Korea. As this study focused on SBA, we included only patients with primary pathologi-

cally confirmed SBA and excluded those with other types of SB cancer, such as carcinoid or lymphoma. In addition, according to the study's inclusion criteria, only patients with follow-up of at least 4 weeks after diagnosis were included. Patients with SBA involving the duodenum were excluded, as they are treated differently from patients with SBA involving other sites, along with having worse survival outcomes. Among patients with SBA, those who had been diagnosed with CD were identified. Thereafter, the patients were classified into two groups: CD-associated SBA and sporadic SBA groups.

According to the National Comprehensive Cancer Network guidelines,³⁴ patients with SBA followed treatment and follow-up strategies, regardless of CD association. Briefly, individuals with localized SBA underwent segmental resection of the involved small bowel with *en bloc* lymph node removal. In cases with an additional microsatellite instability/mismatch repair status, fluoropyrimidine-based adjuvant chemotherapy was considered for patients with stage II or III. In patients with metastatic SBA, palliative chemotherapy was recommended. In addition, in case of malignant SB obstruction, palliative diversion or stenting was done. In terms of surveillance, every patient with SBA visited the centers every 6 months for 2 years, and every 12 months for 3 to 5 years if no recurrence was detected. In every visit, abdominopelvic and chest computed tomography (CT) were performed, and carcinoembryonic antigen levels were checked, for disease evaluation. The intervals could be shortened if recurrence was suspected. During adjuvant or palliative chemotherapy, patients visited the center every month to evaluate chemotherapy-related complications.

2. Data collection and analysis outcomes

Baseline demographics, smoking history, family history of cancer, Charlson comorbidity score,³⁵ and cancer-specific data including date of diagnosis, disease location, histological grade and differentiation, initial stage based on the eighth edition of the American Joint Committee on Cancer (AJCC) staging system,³⁶ and treatment data were collected from the patients' electronic medical records. Among patients with CD-associated SBA, additional data including date of CD diagnosis, age at CD onset, disease location/behavior based on the Montreal classification (L1, L2, L3/B1, B2, B3, and p [perianal disease modifier]),³⁷ treatment of CD, and CD-related bowel resection history were collected. For survival analysis, mortality and recurrence data were also collected.

The primary outcome was OS of sporadic and CD-associated SBA groups, and the secondary outcomes were disease-free survival (DFS) and risk factors associated with

survival. The OS was defined as the time from diagnosis of SBA to death from any cause, and the DFS was defined as the time from diagnosis of SBA to the first recurrence or death. Stage-stratified OS was analyzed between two groups, and DFS was investigated only among the SBA patients who underwent curative-intent surgery with or without adjuvant therapy.

Ethical approval for the acquisition of data was obtained from the institutional review board of each center (IRB numbers: Asan Medical Center [2021-1119] and Seoul National University Hospital [H-2111-120-1273]). As this study was a retrospective study using medical record review, informed consent was waived.

3. Statistical analyses

Baseline characteristics were compared between the CD-associated SBA and sporadic SBA groups. Categorical variables were compared using the Fisher test or the chi-square test, and continuous variables were compared using the two-independent-sample t-test. The Kaplan-Meier method was used to estimate OS in the two groups. Univariate and multivariate analyses with a backward elimination method were performed using the Cox proportional

hazard models to test for a group effect on mortality. Hazard ratios (HRs), and the corresponding 95% confidence intervals (CIs) were calculated. With the interest of HR of CD, CD was included in multivariate analysis regardless of univariate analysis. For missing data, a single imputation method was used before multivariate analysis. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using R (version 3.6.3; R Core Team, Vienna, Austria).

RESULTS

1. Baseline characteristics

The baseline demographic data of the patients are shown in Table 1. Of 128 patients with SBA, 115 were classified into the sporadic SBA group and 13 were classified into the CD-associated SBA group. The overall median follow-up duration was 34.5 months (range, 27 days to 230 months). The median age at SBA diagnosis was 56.0 years (interquartile range, 47.0 to 64.5 years) in the sporadic SBA group and 49.0 years (interquartile range, 44.0 to 58.0 years) in the CD-associated SBA group, although the dif-

Table 1. Baseline Patient Demographics

Variable	Sporadic SBA (n=115)	CD-associated SBA (n=13)	p-value
Age at SBA diagnosis, yr	56.0 [47.0–64.5]	49.0 [44.0–58.0]	0.100
Male sex	77 (67.0)	9 (69.2)	>0.999
Charlson comorbidity score ≥ 2	62 [53.9]	4 [30.8]	0.197
Smoking			0.752
Never smoker	73 [63.5]	10 [76.9]	
Current smoker	16 [13.9]	1 [7.7]	
Ex-smoker	22 [19.1]	2 [15.4]	
Unknown	4 [3.5]	0	
Family history of cancer	39 [33.9]	3 [23.1]	0.630
Location			0.016
Jejunum	85 [73.9]	5 [38.5]	
Ileum	26 [22.6]	7 [53.8]	
Indistinguishable (from jejunum to ileum)	4 [3.5]	1 [7.7]	
Histologic differentiation*			0.043
Well/moderately differentiated	91 [79.1]	6 [46.2]	
Poorly differentiated	17 [14.8]	6 [46.2]	
AJCC stage [†]			0.929
Stage I	3 [2.6]	0	
Stage II	37 [32.2]	5 [38.5]	
Stage III	33 [28.7]	4 [30.8]	
Stage IV	39 [33.9]	4 [30.8]	
Treatment			0.532
Curative operation	20 [17.4]	1 [7.7]	
Curative operation+adjuvant CTx	54 [47.0]	8 [61.5]	
Palliative operation±palliative CTx	41 [35.7]	4 [30.8]	

Data are presented as median (interquartile range) or number (%).

SBA, small-bowel adenocarcinoma; CD, Crohn's disease; AJCC, American Joint Committee on Cancer; CTx, chemotherapy.

*Pathologic data were available in 108 patients with sporadic SBA, and 12 patients with CD-associated SBA, respectively; [†]Staging data of three patients with sporadic SBA were missing.

Table 2. Demographic Data of Patients with CD-Associated SBA

Patient no.	Sex	CCS	Smoking	FHx	CD				SBA			
					Duration, yr	Location*	Behavior*	Medication	Location	Histological diff	Stage [†]	Treatment
1	F	0	Never	0	14	L1	B2	5-ASA	Jejunum	P/D	II	Curative op+adj CTx
2	F	0	Never	0	6	L1	B2	5-ASA, IM	Ileum	P/D	II	Curative op+adj CTx
3	M	0	Never	0	15	L1	B2	5-ASA	Ileum	M/D	III	Curative op+adj CTx
4	M	2	Never	0	0	L3	B2	5-ASA, IM, IFX	Ileum	W/D	II	Curative op+adj CTx
5	M	2	Current	0	21	L3	B2	5-ASA	Ileum	M/D	III	Curative op+adj CTx
6	M	2	Never	0	0	L3	B1	5-ASA	Jejunum	P/D	IV	Palliative CTx
7	M	0	Never	1	12	L3	B3	5-ASA, IM	Ileum	P/D	III	Curative op+adj CTx
8	F	0	Never	0	16	L3	B3p	5-ASA, IM, IFX	Jejunum	Undetermined	IV	Palliative op
9	M	1	Ex-smoker	1	13	L1	B2p	5-ASA, IM	Ileum	M/D	IV	Palliative op+CTx
10	M	1	Ex-smoker	0	1	L1	B2	5-ASA, IM, IFX	Undetermined	M/D	II	Curative op+adj CTx
11	M	2	Never	1	2	L1	B2	5-ASA, IM	Jejunum	M/D	IV	Palliative op+CTx
12	F	0	Never	0	2	L3	B2p	5-ASA, IFX	Jejunum	P/D	II	Curative op
13	M	0	Never	0	23	L3	B2	5-ASA, IM	Ileum	P/D	III	Curative op+adj CTx

CD, Crohn's disease; SBA, small-bowel adenocarcinoma; CCS, Charlson comorbidity score; FHx, family history of cancer; diff, differentiation; F, female; M, male; 5-ASA, 5-aminosalicylate; IM, immunomodulator; IFX, infliximab; P/D, poorly differentiated; M/D, moderately differentiated; W/D, well differentiated; op, operation; adj, adjuvant; CTx, chemotherapy.
^{*}Based on the Montreal classification; [†]Based on the American Joint Committee on Cancer eighth staging system.

ference was not statistically significant ($p=0.100$). Both groups showed a male predominance. The sporadic SBA group included more patients with Charlson comorbidity score ≥ 2 than the CD-associated SBA group, with no statistical significance (53.9% vs 30.8%, $p=0.197$). In terms of the SBA location, the most affected site was the jejunum (73.9%) in the sporadic SBA group and the ileum (53.8%) in the CD-associated SBA group ($p=0.016$). With respect to histological differentiation, a poorly differentiated histology was more common in the CD-associated SBA group (46.2%) than in the sporadic SBA group (14.8%) ($p=0.043$). Other variables including smoking history, family history of cancer, initial stage according to the AJCC staging system, and treatment strategy were not different between the two groups.

2. Detailed demographic data in the CD-associated SBA group

The detailed demographic data of patients in the CD-associated SBA group are summarized in Table 2. During a median CD duration of 12 years, seven patients (53.8%) had ileocolonic (L3) and six patients (46.2%) had ileal (L1) CD, but none had colonic CD. Twelve patients (92.3%) had a stricturing/penetrating behavior, whereas one had an inflammatory behavior. In terms of treatment of CD, nine patients received combination therapy with 5-aminosalicylate (5-ASA) and an immunomodulator or biological agent.

3. Survival outcomes

In survival analysis, the OS of patients with CD-associated SBA was lower than that of patients with sporadic SBA, without statistical significance (1-year OS, 76.2% vs 85.5%; 2-year OS, 45.7% vs 70.8%; 5-year OS, 34.3% vs 54.0%;

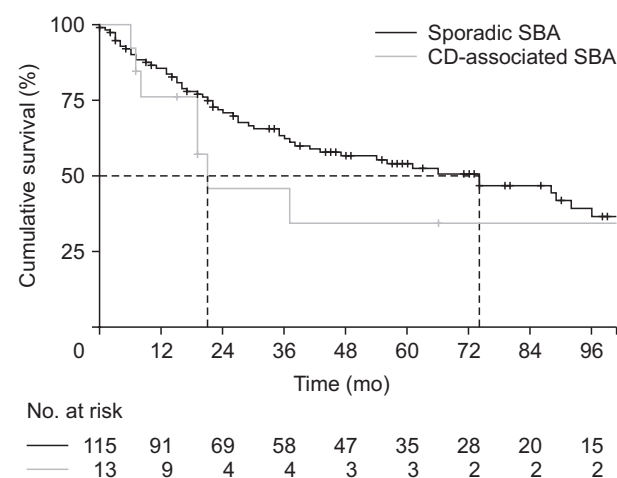


Fig. 1. Unadjusted overall survival according to group. SBA, small-bowel adenocarcinoma; CD, Crohn's disease.

$p=0.370$) (Fig. 1). The median survival time was 74 months in the sporadic SBA group and 21 months in the CD-associated SBA group. When stratified by initial disease stage, among patients with stage I/II disease the adjusted OS appeared not to be different between the two groups ($p=0.530$) (Fig. 2A). However, among patients with stage III/IV disease, the adjusted OS appeared to be lower in the CD-associated SBA group (median survival, 19 months) compared to the sporadic SBA group (median survival, 43 months) ($p=0.029$) (Fig. 2B). All patients with CD-associated SBA died within 2 years after the diagnosis. The DFS among patients with SBA with curative therapy was also analyzed, and the CD-associated SBA group showed a numerically lower DFS without clinical significance (1-year DFS, 63.5% vs 80.7%; 2-year DFS, 50.8% vs 71.3%; 5-year DFS, 33.9% vs 69.4%;

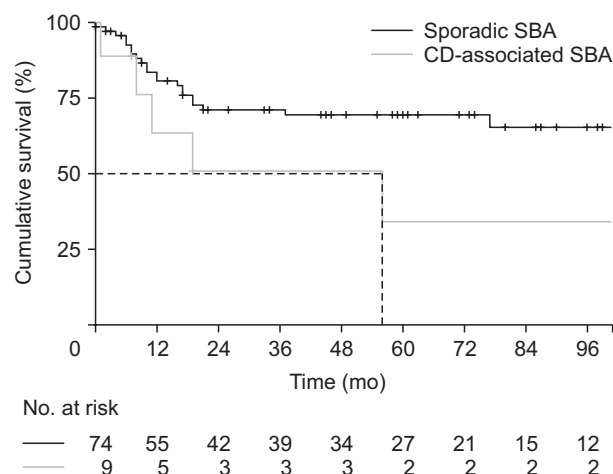


Fig. 3. Disease-free survival according to group. SBA, small-bowel adenocarcinoma; CD, Crohn's disease.

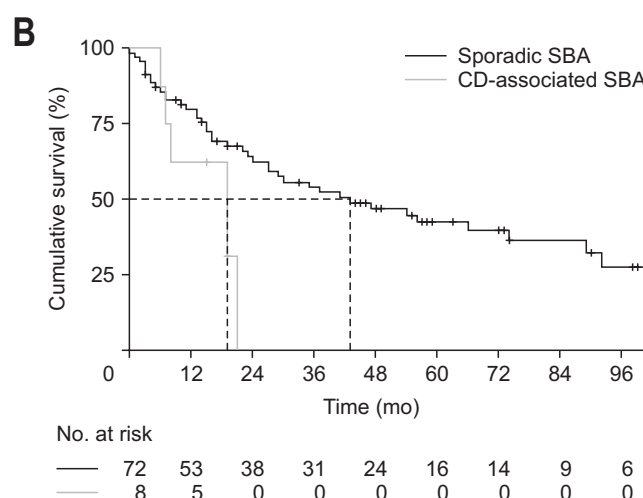
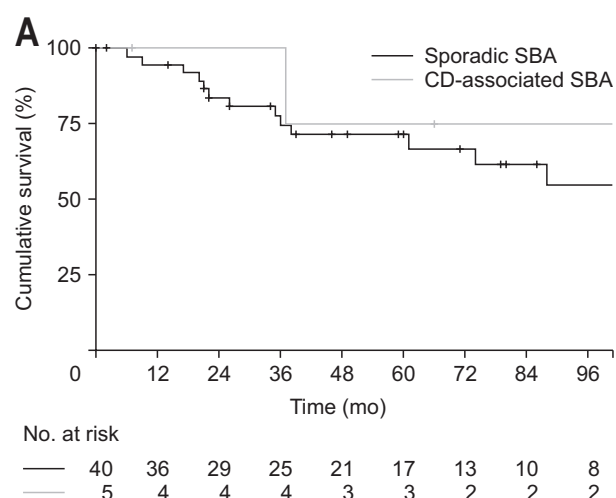


Fig. 2. Adjusted overall survival stratified by stage: (A) stage I/II and (B) stage III/IV. SBA, small-bowel adenocarcinoma; CD, Crohn's disease.

Table 3. Cox Proportional Hazard Models for Risk of Mortality

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Crohn's disease	1.449 [0.657–3.195]	0.358	2.308 [1.011–5.266]	0.047
Age at SBA diagnosis (≥ 65 yr)	2.139 [1.222–3.743]	0.008	2.766 [1.551–4.934]	0.001
Female sex	1.349 [0.803–2.267]	0.259		
Charlson comorbidity score ≥ 2	1.199 [0.725–1.983]	0.479		
Smoking (ref. never smoker)	1	0.083		
Current smoker	0.940 [0.443–1.995]	0.871		
Ex-smoker	0.402 [0.181–0.897]	0.026		
Family history of cancer	0.673 [0.379–1.198]	0.178		
Location (ref. jejunum)	1	0.478		
Ileum	1.411 [0.800–2.488]	0.234		
Indistinguishable (ileum to jejunum)	0.868 [0.119–6.339]	0.889		
Histological differentiation (ref. well/moderately differentiated)				
Poorly differentiated	1.364 [0.719–2.588]	0.341		
AJCC stage (ref. stage I/II)				
Stage III/IV	2.689 [1.474–4.907]	0.001	3.151 [1.723–5.761]	<0.001

HR, hazard ratio; CI, confidence interval; SBA, small-bowel adenocarcinoma; ref., reference; AJCC, American Joint Committee on Cancer.

$p=0.097$) (Fig. 3). The median DFS time of patients with CD-associated SBA was 56 months.

4. Risk factors associated with mortality

In the univariate analysis, older age (≥ 65 years) at SBA diagnosis (HR, 2.139; 95% CI, 1.222 to 3.743; $p=0.008$) and initial AJCC stage III/IV (HR, 2.689; 95% CI, 1.474 to 4.907; $p=0.001$) were statistically significant factors (Table 3). However, in further multivariate analysis, CD (HR, 2.308; 95% CI, 1.011 to 5.266; $p=0.047$), older age (≥ 65 years) at SBA diagnosis (HR, 2.766; 95% CI, 1.551 to 4.934; $p=0.001$), and AJCC stage III/IV (HR, 3.151; 95% CI, 1.723 to 5.761; $p<0.001$) were risk factors for mortality.

DISCUSSION

To our best knowledge, this is the first Asian study to investigate the characteristics, survival, and risk factors for mortality in patients with CD-associated SBA and sporadic SBA, along with detailed features of CD. The CD-associated SBA group showed a predominance of ileal involvement and a higher percentage of poorly differentiated histology than the sporadic SBA group. OS seemed to be lower in the CD-associated SBA group, albeit with no statistical significance. However, when stratified by disease stage, the adjusted OS of the CD-associated SBA group appeared to be lower in patients with advanced disease stage (AJCC stage III/IV, $p=0.029$). With respect to DFS, the CD-associated SBA group did not show a significant difference from the sporadic SBA group. In multivariate analysis, CD, older age (≥ 65 years) at SBA diagnosis, and advanced disease stage (AJCC stage III/IV) were independent risk factors associated with mortality.

In previous studies, the median age at SBA diagnosis was younger in patients with CD-associated SBA, ranging from 43 to 62 years,^{5,9,19} and some studies reported a 20 years older age in the sporadic SBA group.⁷ In this study, the median age at SBA diagnosis was also younger in the CD-associated SBA group (49.0 years), although no significance was found. In contrast with the female predominance in patients with CD-associated SBA in previous studies,^{5,9} both groups in this study included more male patients. This is in line with other studies,^{7,33} although it may be a reflection of the male predominance of CD (male-to-female ratio, 2.5:1) in Korea.³⁸ The lack of a difference in age at SBA diagnosis between the two groups may have resulted from the unique national medical insurance system in Korea, which provides easy access to medical services with low costs, along with the relatively small sample size of this study.

In terms of the SBA location, many studies reported ileal predominance in patients with CD-associated SBA, whereas patients with sporadic SBA tended to have a more even distribution of jejunal and ileal involvement.^{5,9,10,20} Likewise, the most common site was the ileum in the CD-associated SBA group in this study, although the actual difference from the number of patients with jejunal SBA was small (only two patients). In addition, in the sporadic SBA group, the number of patients who showed jejunal involvement was almost three times the number of patients with ileal SBA. This difference may have resulted from the small cohort size and referral bias. With respect to histological differentiation, poorly differentiated SBA was more common in the CD-associated SBA group than in the sporadic SBA group, which is in line with previous reports.^{9,10}

Meanwhile, patients with advanced disease stage were predominant in both groups. As the diagnosis of SBA is challenging,³⁹ owing to the limitations of non-invasive modalities such as abdominal CT or magnetic resonance imaging and because of the difficulty in obtaining adequate tissue samples from affected bowel segments, long-standing, undiagnosed SBA may progress with vague symptoms. Further, a long duration of CD has been suggested as one of the strongest risk factors for SBA.² In a French study, the cumulative risk of patients with CD-associated SBA was 0.2% and 2.2% after 10 and 25 years of ileal CD, respectively.⁵ Considering that previous studies reported a median CD duration of 15 to 25 years among patients with CD-associated SBA,^{5,14,33} our data (median CD duration, 12 years) are consistent with prior results.

With respect to OS, previous studies in patients with CD demonstrated a 5-year OS rate of approximately 30% to 40%, which was not different from the OS rate of sporadic cases.^{5,6,9,10} In this study, the unadjusted OS rate of patients with CD-associated SBA was not significantly different from that of patients with sporadic SBA. In survival curves, the 5-year OS rate of patients with CD-associated SBA was 34.3%. However, when stratified by disease stage, the OS of patients with CD-associated SBA seemed lower than that of patients with sporadic SBA, among those with an advanced disease stage. This result is in line with several reports,^{14,31-33} but is in contrast to a recent large population-based study by Fields *et al.*⁹ In our study, more patients had a poorly differentiated histology and an advanced disease stage, which might have discouraged both patients and clinicians from selecting aggressive treatments for CD. The potential reason for the poorer prognosis of CD-associated SBA is assumed to be missed diagnosis. As it is difficult to distinguish CD-associated SBA from acute exacerbation of CD or stricturing CD, the initial SBA symptoms could be neglected or overlooked as CD-related symptoms. Even

with suspicion, indirect imaging modalities such as CT or magnetic resonance enterography are not enough for definite diagnosis, and the low accessibility to the involved lesion makes the diagnosis much harder. Therefore, undiagnosed CD-associated SBA for long time may result in poorer prognosis.

The previously suggested risk factors associated with SBA in patients with CD included location (distal jejunum/ileum), behavior (stricturing or penetrating), long disease duration, young age at diagnosis, male sex, use of steroids and immunomodulators, SB bypass loops, strictureplasties, and environmental factors.²⁹ Meanwhile, the reported protective factors were SB resection and use of 5-ASA for >2 years in a case-control study.³⁰ In this study, in the CD-associated SBA group, four patients treated with only 5-ASA developed SBA. Most patients showed a stricturing or penetrating phenotype with SB involvement of CD, although one patient (patient 6) showed non-stricturing/penetrating disease. Patient 6 had ileocolonic CD, and SBA was diagnosed after 8 months of CD treatment with 5-ASA. Taking into consideration the inflammation–dysplasia–carcinoma sequence, it can be assumed that some patients with CD-associated SBA may have long-standing, undiagnosed CD, that was only identified around the time of the SBA diagnosis. As the evaluation of the SB at CD diagnosis is dependent on indirect imaging modalities, such as CT or magnetic resonance enterography,⁴⁰ instead of direct observation of entire SB segments through enteroscopy,^{41,42} subtle but chronic mild inflammation in the SB may be overlooked on imaging studies. In addition, a different pathogenesis from the previously well-defined neoplastic transformation, such as microsatellite instability or K-ras mutations, may contribute to the development of SBA in patients with CD.²⁹ Recently, a next-generation sequencing study by Liao *et al.*⁴³ demonstrated different genetic mutation profiles of *IDH1*, *SMAD4*, *FBXw7*, and *SMARCB1* in patients with CD-associated SBA, suggesting different mechanisms of carcinogenesis. Further studies aimed at identifying the specific pathogenesis of CD-associated SBA may help establish targeted surveillance and treatment.

In the multivariate analysis to identify risk factors for SBA mortality, we found that older age (≥ 65 years), advanced disease stage (AJCC stage III/IV), and CD were independent risk factors for decreased survival. Older age at SBA diagnosis and advanced stage of SBA were already suggested as risk factors in the study by Wieghard *et al.*¹⁰ However, whether CD itself is a risk factor for survival remains controversial. Using the data from a U.S. National Cancer Database Registry, Fields *et al.* reported similar OS between patients with CD-associated SBA and those with sporadic SBA and that CD was not an independent

risk factor for death (HR, 1.01; 95% CI, 0.99 to 1.02).³⁴ By contrast, in a bi-national population-based cohort study from Sweden and Denmark, the rate of death from SB cancer was 7-fold higher in patients with CD, with an overall adjusted HR of death from SB cancer of 6.59 in patients with CD (95% CI, 4.74 to 9.15).²⁰ In this study, CD was not significant in univariate analysis; however, we further included CD in multivariate analysis, and CD turned out to be a significant factor for survival. Although the result should be interpreted with caution, possible synergism among CD, older age, and advanced stage may result in a significant impact on survival of SBA. From this perspective, this can provide supporting evidence for the necessity of structured surveillance of SBA in high-risk CD patients, such as older patients with CD. On the other hand, referral bias with overestimated HRs may exist, as a result of the relatively small sample size. Further national population-based cohort studies may help clarify the HR of SBA mortality in patients with CD.

The strength of this study was being the first Asian study to compare the characteristics of CD-associated SBA and sporadic SBA while investigating the survival outcomes and clarifying the risk factors associated with mortality. In addition, we retrospectively reviewed medical records from the two largest tertiary referral centers in Korea. This enabled a meticulous review of the characteristics of patients with CD-associated SBA, including the duration of CD, SBA location and behavior, medication history, prior history of bowel resection, pathological information, and survival data (recurrence or death). To our knowledge, our study is the first to report data on the DFS of patients with CD-associated SBA or sporadic SBA. In addition, the overall median follow-up duration of 34.5 months (range, 27 days to 230 months; >19 years) is relatively longer than that of previous studies.

However, this study had some limitations. As mentioned above, this was a retrospective, referral center cohort study. Thereby, we could only evaluate the association between risk factors and CD, not the causal relationship of certain factors. In addition, along with the referral bias and small sample size (only 13 patients of CD-associated SBA), issues related to the generalization of our observations and data imbalance remain associated with our study results. This was largely due to the rarity of SBA itself. However, data from the two largest centers in Korea could provide reliable, long-term follow-up data of Korean CD patients. Further, with a small number of patients with CD-associated SBA, subgroup analysis other than OS according to disease stage were not performed. Meanwhile, we excluded duodenal adenocarcinoma, and this might have affected the survival outcomes to some extent. However, excluding duodenal SBA might have helped eliminate heterogeneity

and improved the matching of the CD-associated SBA and sporadic SBA groups.

In conclusion, this study showed no difference in OS between patients with CD-associated SBA and those with sporadic SBA. However, among patients with advanced disease stage, those with CD-associated SBA showed decreased survival. In particular, older age, advanced disease stage, and CD were identified as independent risk factors for mortality. Further studies clarifying the clinical efficacy of surveillance in the high-risk group of patients with CD are warranted.

CONFLICTS OF INTEREST

J.P.I. is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: K.K., K.C., S.J.K., S.H.P. Data acquisition: K.K., K.C., S.W.H. Data analysis and interpretation: K.K., K.C., J.P.I., B.D.Y., J.S.K., K.J.P. Drafting of the manuscript: K.K., K.C., S.J.K., S.H.P. Critical revision of the manuscript for important intellectual content: J.P.I., J.S.K., S.K.Y., S.J.K., S.H.P. Statistical analysis: K.K., K.C., J.P.I., B.D.Y., J.S.K., K.J.P. Study supervision: S.J.K., S.H.P. Approval of final manuscript: all authors.

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