Prognosis of Ulcerative Colitis Colorectal Cancer *vs.* Sporadic Colorectal Cancer: Propensity Score Matching Analysis

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Abstract

Background: Ulcerative colitis (UC) harbours a high risk of UC-associated colorectal cancer (UCCC), which is important cause of morbidity and mortality in patients with inflammatory bowel disease. Overall survival (OS) of patients with UCCC has not been addressed well in the literature. Thus, we compared oncologic outcome of UCCC and sporadic colorectal cancer (SCC) using propensity score matching analysis.

Methods: Propensity score matching was performed for 36 patients, a 1:1 matching method stratified into 18 in UCCC and 18 patients in SCC. Matched variables were sex, age, body mass index, tumour stage, histology, preoperative carcinoembryonic antigen (CEA) level, and adjuvant treatment status. Patients with SCC or UCCC were retrospectively retrieved from our database from March 2000 to December 2015. All patients had undergone either oncological segmental resection or total proctocolectomy.

Results: The majority of cancers were found in the sigmoid colon. Total proctocolectomy was performed only in the UCCC group; however, half of the UCCC group underwent a standard operation. Five cases of postoperative complication occurred within six months in the UCCC group compared to one case in the SCC group. There was no significant difference in recurrence rate (p=0.361) or OS (p=0.896) between the arms.

Conclusion: UCCC showed more postoperative complications than SCC, and equivalent oncology outcome, however the difference was not statistically significant. This study represents an experience of a single institution, thus further randomized studies are required to confirm.

Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of the large bowel for which the aetiology is not fully understood [1]. This disease harbours a high risk of associated colorectal cancer (UCCC). This is the most important cause of morbidity and mortality in patients with inflammatory bowel disease (IBD) [2], accounting for 10-15% of deaths in IBD patients [3]. However, the real impact of colorectal cancer (CC) is still debated in the literature. Fifteen years ago, Eaden et al. published a meta-analysis reporting that the cumulative risk of CC in patients with UC was 2% at 10 years [4]. A later meta-analysis by Lutgens et al. reviewed eight studies published from 1988 to 2009 and showed that the risk of CC was increased in IBD but was not as high as reported in earlier studies; the pooled standardised incidence rate in their study was 1.7 [5]. Recently, Castano-Milla et al. published their systemic review and meta-analysis [6], in which they concluded that the risk of developing CC among patients with UC has decreased steadily over the last six decades and was 1.58 per 1,000 patient-years. Another recent meta-analysis showed a 2.4 fold higher rate of CC in UC patients compared to the overall population [7].

Previous studies have reported several clinical and pathogenetic differences between sporadic CC (SCC) and UCCC. It is known that CC occurs about 30 years earlier than UCCC in UC patients [4]. UC patients are known to have higher rates of multifocal, right-sided tumours and mucinous or signet ring cell carcinomas, which are associated with poor prognosis [8-10].

The survival of patients with UCCC was not discussed in previous reports. Early studies showed five -year survival rates up to 30 % [11-14]; however, the overall survival (OS) for patients with SCC at the same period was similar. Recent studies have shown much higher survival rates and no significant difference between UCCC and SCC patients [15,16]. In contrast, some other studies have reported poorer survival for UCCC patients than for patients with SCC [8,17-20]. The authors explained the poorer survival in UCCC patients by an unfavourable stage distribution, since a greater proportion of UCCC patients had distant metastasis at the time of cancer diagnosis. The existing data are conflicting and heterogeneous, as patient collectives vary regarding factors such as follow-up period, matching criteria, and stage distribution.

Because of the relatively low prevalence, little is known about the differences in prognosis between SCC and UCCC. In this study, we compared two cohorts of UCCC and SCC patients in terms of long-term outcome and recurrence rate using propensity score matching analysis.

Patients and Methods

Patients

Data for all patients who underwent surgical treatment for UCCC and SCC in the Department of Surgery at Yonsei University between March 2000 and December 2015 were entered into prospective databases. All patients diagnosed with colon cancer due to sporadic or ulcerative colitis have been enrolled in our analysis. However, to achieve an accurate analysis we carried out propensity cross match analysis. A total of 36 patients divided according to aetiology of colon cancer into 18 patients by UCCC and 18 patients were SCC. All patients have been matched following these criteria: age at surgery (± 5 years), sex, body mass index (BMI), tumour stage (according to American joint commission for cancer), histology, preoperative CEA level, and adjuvant treatment. Patient demographics, co-morbidities, detailed operative information, histopathologic tumour features, and follow-up data were obtained by medical record review. The primary outcome for comparison was OS. Recurrent disease was defined if a suspected lesion became apparent by imaging modalities after a period of 6 months of undetectable disease, including local recurrence in the same location as the primary tumour, regional recurrence, and distant recurrence in other organs such as liver and lungs. Board-certified colon and rectal surgeons at a tertiary referral centre participated in performing designed surgery. Resections for CC included segmental proctectomy or extended resection by total proctocolectomy.

Statistical analysis

Categorical variables are expressed as percentage and compared by Fisher's exact test or Chi-square test as appropriate. Continuous variables are presented as mean ± standard error of the mean or median and interquartile range (IQR) per group and are compared using two-tailed Student's t-test. Survival curves for 1, 3, 5, and 10 years were generated using the Kaplan-Meier method, and survival was compared by log rank and Breslow tests. Survival percentages per measured time point are reported with 95% confidence interval (CI). Significance was set at $p<0.05$. Calculations were performed using SPSS Statistics for Windows.

Results

Out of 36 patients, 18 (50%) had SCC and 18 (50%) had UCCC. Patient characteristics of BMI, age, sex, pathological stage, preoperative CEA level, and tumour location were matched in both groups (Table 1). Adjuvant chemotherapy was administered equally to both groups. The majority of cancers were found in the colon: 15 (83.3%) for each of SCC and UCCC. Most patients in the SCC group presented with stage II cancer (9 patients, 50%), whereas in the UCCC group, 6 patients (33.3%) had stage II and 7 (38.9%) had stage III disease. Total proctocolectomy was performed significantly more often in the UCCC group (9 *vs.* 0 patients, p=0.001). UCCC showed more postoperative complications than SCC (5 *vs.* 1), although this was not significant (p=0.634). A relatively higher local recurrence rate was observed in SCC (5.6% [1 patient] *vs.* 0 in the UCCC group), but the overall recurrence was not significantly differ (p=0.361) (Table 2). There was no significant difference in five-year OS between the two arms (Figure 1).

Variables	Sporadic (n=18)	UC (n=18)	P-value
Age at surgery (years)	52 (30-73)	51 (31-68)	0.866
Sex			0.735
Male	7 (38.9%)	8 (44.4%)	
Female	11 (61.1%)	10(55.6%)	
BMI (kg/m2)	23.23 ± 3.36	22.38 ± 1.47	0.328
Stage			0.593
1	4 (22.2%)	5 (27.8%)	
2	9 (50%)	6 (33.3%)	
3	5 (27.8%)	7 (38.9%)	
Adjuvant chemotherapy			1
Yes	12 (66.7%)	12 (66.7%)	
No	6 (33.3%)	6 (33.3%)	
Histology			0.388
WD	3 (16.7%)	5 (27.8%)	
MD	13 (72.2%)	9 (50%)	
PD	2 (11.1%)	4 (22.2%)	

Carcinoembryonic antigen (CEA)	2.27 ± 2.28	2.55 ± 1.79	0.684
Location			1
Rectum	3 (16.7%)	3 (16.7%)	
Colon	15 (83.3%)	15 (83.3%)	
All values are represented as n (%) or mean ± SD			
UC-Ulcerative colitis; WD-Well differentiated; MD-Moderately differentiated; PD-Poorly differentiated			

Table 1: Characteristics and perioperative findings of patients diagnosed with colorectal cancer.

Variables	Sporadic CC (n=18)	UCCC (n=18)	P value
Operation method			0.735
Open	8 (44.4%)	7 (38.9%)	
MIS	10 (55.6%)	11 (61.1%)	
Operation name			0.001
Total proctocolectomy with end ileostomy	0 (0%)	1 (5.6%)	
Total proctocolectomy with J-pouch anal anastomosis	0 (0%)	4 (22.2%)	
Total proctocolectomy with ileo-anal anastomosis	0 (0%)	4 (22.2%)	
Others	18 (100%)	9 (50%)	
Complication			0.624
Obstruction	1 (5.6%)	4 (22.2%)	
Rectovaginal fistula	0 (0%)	1 (5.6%)	
Recurrence			0.361
Local	1 (5.6%)	0 (0%)	
Systemic	2 (11.1%)	2 (11.1%)	
All values are represented as n (%).			
MIS-Minimal invasive surgery; UC-Ulcerative colitis; UCCC -Ulcerative colitis-related colorectal cancer			

Table 2: Operative variables and short- and long-term results of patients undergoing colonic or rectal resection.

Discussion

In this study, we compared the prognosis of patients with UCCC or SCC in a matched pair analysis that including one of the largest cohorts of UCCC patients to date [15,16]. Prognosis was similar in the two groups, with a trend toward higher recurrence rate in the SCC group.

UCCC patients are typically younger and more frequently have multiple cancerous lesions and a macroscopically permeating pattern of spread, including mucinous or signet ring cell carcinomas, compared with SCC. The advanced stage at presentation results in a less favourable outcome for UCCC patients [2,7,8].

Chronic inflammation leads to the activation of sequins, which in turn leads to CC in UC patients. Colonic mucosa in UC exhibits high levels of chromosomal abnormalities clustered in regions of histological abnormality, and genomic derangements are a prominent feature of preinvasive neoplasia [1]. The same genetic and signalling pathways involving Wnt, β-catenin, K-ras, p53, and transforming growth factor (TGF)-β can be found in SCC and UCCC; however, a difference in activation timing between SCC and UCCC has been reported [3]. Mutations in p53 occur early in the adenoma-carcinoma sequence and are often detected in non-dysplastic or indefinite dysplasia in UC, whereas p53 mutations occur in the late phase in sporadic adenoma [21]. Microsatellite instability (MSI) is also relatively frequent in non-dysplastic inflamed epithelia, and transforming growth factor β receptor type II (TGFβRII) is one of the genes targeted by the MSI process in UCCC. Hypermethylation of hMLH1, p16INK4a, and p14ARF seems to precede dysplasia and contribute to the genetic alterations in UCCC [22]. Kinugasa et al. also showed that expression of claudin-1 was increased in UCCC and dysplasia compared with normal mucosa and is likely to be involved in neoplastic progression in UC patients [23].

Some previous studies have shown worse oncological outcomes in the UCCC patient group [8,20,24]. In a Japanese nationwide study,

Watanabe et al. assessed 121 patients who had undergone surgery for UCCC. They found that, compared with patients with SCC, those with UCCC were younger and had a higher proportion of multiple cancer lesions, higher proportions of morphologically superficial type lesions and invasive type lesions, and higher proportions of mucinous or signet ring cell carcinomas. For stage III disease, patients with UCCC had a poorer survival rate than those with SCC (43.3% *vs.* 57.4%, P=0.0320); however, the OS was similar in earlier stages [8]. The UCCC-specific factors and different clinicopathologic patterns mentioned above are thought to result in an unfavourable prognosis [8,25-27]. In a Danish cohort study by Jensen et al. 279 UCCC patients were compared to 71,259 SCC patients. The OS was significantly worse in the UCCC group. The negative effect of UC on the prognosis of CC was more pronounced in the first year after cancer diagnosis, in patients diagnosed with CC before the age of 70 years, in patients with UC duration of eight years or more, and in cancers with advanced or unknown stage [20]. In a recent matched pair analysis, 33 patients with inflammatory bowel disease-associated CC had a significantly reduced and markedly lower OS rate, as well as a notably increased recurrence rate, compared to sporadic CRC patients (48.6 *vs.* 67.1 %, respectively) [24]. A single-centre retrospective study performed in 2016 compared OS and surgical technique in 27 patients with UC and rectal cancer and 54 patents with sporadic rectal cancer [15]. UCCC patients undergoing proctectomy demonstrated reduced disease-free survival (DFS) compared with those undergoing proctocolectomy and patients with sporadic rectal cancer undergoing proctectomy. The authors concluded that proctocolectomy should be considered the preferred surgical approach for colitis-associated rectal cancer.

Figure 1: Kaplan–Meier estimates of overall survival and 5- and 10-year overall survival rates of 18 patients with ulcerative colitis-associated carcinoma and 18 patients with sporadic colorectal carcinoma. SCC-Sporadic colorectal cancer; UCCC-Ulcerative colitis-related colorectal cancer, SCC 114.05 ± 11.13, 95% CI (92.23–135.87) UCCC 147.89 ± 18.55, 95% CI (111.53–184.24) Log rank: p=0.896 Breslow: p=0.932.

Our study and some other retrospective single-centre studies showed no difference in OS [19,28–30]. Our study was in agreement with the survival results of a Finnish study from 1998 that compared 33 UCCC patients to 122 patients with non-UCCC [19]. In two smaller retrospective case-matched cohort studies performed in a single tertiary centre by Kiran et al. [28] and Delaunoit et al. [29], the authors found no difference in OS between patients with IBD and CC with those with SCC. In a later study by Delaunoit, higher tumour grades and mucinous differentiation were more frequent among patients with UCCC. Kiran et al. [28] found no difference between two groups of UCCC and SCC patients in terms of local recurrence, DFS, or OS. In a recent large study from Germany, the authors matched UCC and SCC patients 1:1 [30]. Although they found more of the above mentioned risk factors in the UCCC group, the oncological outcome was the same in both groups. In a subgroup analysis of UCCC patients, female sex was associated with a significantly better prognosis. The authors assumed that oestrogens play a protective role in UCCC carcinogenesis.

Interestingly, some population-based studies have shown decreased mortality in patients with UCCC compared to those with UC. The authors explain this finding by long-term usage of 5-ASA [31]. The same study showed an increased risk of postoperative complications (postoperative deaths, septicaemia, other abdominal infections) in patients with UCCC. However, our study did not show any significant differences in the rate of complications.

Although total proctocolectomy with ileal pouch-anal anastomosis is the gold standard for UCCC, the pros and cons of rectal mucosectomy are still debated [32,33]. Whether this represents the optimal procedure for UC patients with SCC remains questionable, as the functional quality of life differs substantially between patients with proctocolectomy and those with partial resection. In elderly patients with poor anal function, surgical procedures should obviously be selected based on overall considerations including prognosis of the cancer, degree of inflammation with colitis, and potential requirements for future treatment. Uchino et al. have reported two cases with mild inflammation that underwent segmental colon resection [34]. Some case reports even show the usefulness of prognostic factors for the possibility of segmental resection [5].

Recent studies have shown the importance of surveillance programs in patients with long lasting UC [36-38]. The authors concluded that colonoscopy results in diagnosis of cancer at earlier stages and younger ages. In addition, premalignant conditions can also be identified [36]. Most international guidelines recommend surveillance for UC using colonoscopy every 1-2 years over 8-10 years after the onset of UC diagnosis [39-44].

Our study has some limitations. First, the single centre, relatively small size, and retrospective nature of the study might weaken the significance of our findings. Second, there may be selection bias because not all patients who were diagnosed with UC and CC in the study period were included in the study, although we performed matched analysis for patient sex, age, body mass index, tumour stage, histology, preoperative CEA level, and adjuvant treatment status.

In conclusion, our data suggest that patients with UCCC have the same prognosis as patients with SCC. All other factors related to UC (e.g., UC treatment before and after CC, disease activity and duration) and CC (e.g., aggressive tumours, surgical techniques, and surgical complications), as well as a number of other factors should be investigated in order to rule out confounding factor that might be of prognostic value (e.g., co-morbidity, co-medication, hereditary factors). Therein, well clinical trial is required to address these ongoing debates in the future.
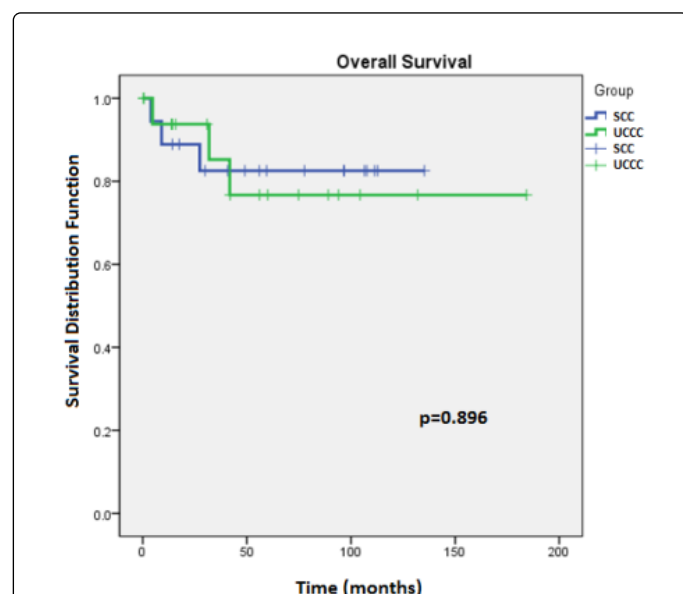
Acknowledgements

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