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Postoperative Survival in Colitis-associated Colorectal Cancer With Ulcerative Colitis in Japan: A Multicenter Analysis

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Abstract. *Background/Aim: The aim of the study was to analyze the postoperative survival of colitis-associated colorectal cancer (CAC) with ulcerative colitis (UC), and the risk factors affecting it. Patients and Methods: A questionnaire including postoperative survival was sent to 88 hospitals that reported CAC patients in the literature up until January, 2006 and to members of the Research Group of Intractable Inflammatory Bowel Disease. Results: The 5-year postoperative overall survival (OS) of 170 CAC patients was 74.2% which was similar to sporadic colorectal cancer in Japan (72.1%). Pathologic TNM stage, histological type, type of surgical procedure (proctocolectomy, segmental resection), and preoperative cancer surveillance were statistically significant factors for OS. By Cox regression analysis, pathologic TNM stage and proctocolectomy were statistically significant prognostic factors for OS. Conclusion: In CAC with UC, the postoperative OS was similar to sporadic colorectal cancer. Pathologic TNM stage and proctocolectomy were confirmed as important prognostic factors.*

Colorectal cancer (CRC) is well known to be associated with longstanding ulcerative colitis (UC) as colitis-associated colorectal cancer (CAC), which derives from an inflamed colonic mucosa. CAC is a major cause of mortality and the incidence of CAC is gradually increasing with an increasing number of patients with longstanding UC in the world (1-3), including Japan.

The radical and standard surgical procedures for CAC are ileal pouch anal anastomosis with mucosectomy (handsewn Ileal pouch anal anastomosis: HS-IPAA) or total proctocolectomy with ileostomy (TPC) due to the possibility of multifocal malignant lesions in the inflamed large bowel. However, stapled ileal pouch anal anastomosis with preservation of the anal canal mucosa (stapled IPAA: S-IPAA) is the alternative procedure, especially for elderly CAC patients (more than 70 years old) without preoperative soiling who are not candidates for HS-IPAA due to inferior anal sphincter function compared to young patients. Segmental resection for CAC, which is not generally alternative due to multifocal malignant lesions, is also occasionally performed in ordinary, non-inflammatory bowel disease centers based on attending surgeon's treatment policy. There were few reports which discussed the comparison of postoperative survival between proctocolectomy (IPAA or TPC) and segmental resection in CAC (4, 5).

It is important to know the results of surgical treatment for CAC to improve the survival rate, because there are not entirely in agreement regarding the difference in postoperative prognosis between CAC and sporadic cancer and the risk factors affecting survival.

We conducted a multicenter analysis on the postoperative survival of CAC patients and the risk factors affecting it.

Patients and Methods

The authors examined case reports of CAC patients with UC in Japan using the key words, "ulcerative colitis" and "colorectal cancer" up until January, 2006. A questionnaire about the features of CAC patients, including postoperative survival, was sent to 88 hospitals from which patients with CAC were reported in the journals. This was done to examine the details of the patients,

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Key Words: Ulcerative colitis, colitis-associated colorectal cancer, postoperative survival.

Table I. *Characteristics of CAC patients (n=189).*

Gender (M/F)	107/81*
Age at onset of UC (yr)	34±15** (10-69) (32)***
Age at diagnosis of CAC	49±15** (21-80) (50)***
Duration of UC	16±8** (0.3-41) (14)***
Extent of UC	
Universal colitis: left sided colitis: proctitis	128:37:4****
Preoperative medical treatment	
5ASA: steroid: IM	146:119:8
Diagnostic procedure of CAC*****	
Clinical symptoms	62 (bloody stool l43, abdominal pain 16 intestinal obstruction 10)
Elevation of tumor marker	15 (CEA 8, CA19-9 7)
Cancer surveillance study (regular examination)	88 (Colonoscopy 77, Barium enema 11)
Colonoscopic examination (irregular examination)	26
Surgical procedure*	
IPAA with mucosectomy	72
Stapled IPAA	34
Total proctocolectomy	31
Others (segmental resection)	51

*One patient: unknown; **Mean±SD; ***Median; ****Twenty cases: unknown; *****Overlapping; ******One patient: unknown.

including postoperative survival, which were not described in the journal. The same questionnaire was also sent to the members' Institutes of the Research Group of Intractable Inflammatory Bowel Disease subsidized by the Ministry of Health, Labor and Welfare of Japan in 2006. Each patient's data were collected anonymously. The data of 201 cases with CAC were collected for the analysis and 12 cases with sporadic cancer or without surgery were excluded. Of the 201 cases, 189 CAC cases were included in this study and analyzed for postoperative survival and the risk factors affecting it.

In 189 CAC cases, sex, age at diagnosis of UC, preoperative medical treatment for UC, diagnostic method for CAC, and pathological features of CAC such as histologic type, pTNM classification, and cancer stage were analyzed. CAC with both components of poorly differentiated adenocarcinoma and mucinous adenocarcinoma were classified as poorly differentiated adenocarcinoma, and CAC with both components of moderately differentiated adenocarcinoma and mucinous adenocarcinoma as mucinous adenocarcinoma.

Cancer surveillance was performed for patients with approximately 10 years of UC history. In this study, cancer surveillance was defined by each author in terms of years from the onset of UC, interval of the examination, and modalities used, which included colonoscopy or barium enema for patients without any symptoms.

Data analysis was performed using the Kaplan–Meier analysis and Cox regression model (SPSS 17.0). The Mann-Whitney *U*-test was also used to compare differences between two independent groups. A p-value of <0.05 was considered statistically significant.

Each patient's data were collected and analyzed anonymously. This study was approved by the ethical committee of Yokohama Municipal Citizen's Hospital.

Results

Patient characteristics (Table I). One hundred and eighty-nine patients with CAC were analyzed. The mean age at onset of UC was 34 years old (range=10-69 years old) and the mean age at diagnosis of CAC was 49 years old (range=21-80 years old). The mean duration from the onset of UC to the diagnosis of CAC was 16 years (range=0.3-40 years). The extent of UC was total colitis in 128 patients, left sided colitis in 37, and proctitis in 4 preoperatively (20 cases: unknown). Of the 4 patients who were diagnosed with proctitis preoperatively, 3 patients had total colitis based on the postoperative pathological examination of the resected specimen and one patient who had proctitis based on the resected specimen, was diagnosed with rectal cancer.

The diagnosis of CAC was based on: cancer surveillance in 88 patients (colonoscopy: 67, barium enema: 11), incidental findings of CAC by periodic colonoscopy for the evaluation of UC in 26 patients, clinical symptoms such as bloody stool and intestinal obstruction in 62 patients, and elevation of serum tumor markers (CEA or CA19-9) in 15 patients.

Surgical procedures included HS-IPAA in 72 patients, stapled IPAA in 34, total proctocolectomy in 31, and segmental resection in 51(one patient: unknown).

Characteristics of CAC (Table II). The most common site of CAC was the rectum (105 cancers, 52%) and sigmoid colon (36 cancers, 18%). Solitary cancer was seen in 129 patients (73%) and multiple cancers in 47 patients (27%) (13 patients: unknown). The histological findings showed that the most common type was well differentiated adenocarcinoma (99 tumors, 50%) and 31 mucinous adenocarcinomas (16%) were found in the resected specimens. The incidence of dysplasia was 63% (90/144 patients with available data).

In terms of histological grading (n=189), pTis was the most common grade (53 cases, 28%) and pT3 andT4 were the second most common grades (39 cases, 20%,

Table II. *Characteristics of CAC (n=189).*

Location of cancer*	Appendix: 1, Cecum: 9, Ascending colon: 20, Transverse colon: 17 Descending colon: 14, Sigmoid colon: 36, Rectum: 105, Anal canal: 8
Number of cancers**	Solitary: 129, Multiple: 47
Configuration(type)***	Protuberant type 39, Localized-ulcerating 20, Infiltrating-ulcerating 15, Diffuse-infiltrating 21, Unclassified 22
Histology*	Well differentiated ad. ca: 99, Moderate: 43, Poorly: 23 Mucinous: 31
Depth of tumor invasion****	Tis: 53, T1: 32, T2: 28, T3: 39, T4a: 29, T4b: 10
pTMN classification******	Stage 0: 45, I: 41, II: 32, III: 31, IV: 16

*Overlapping; **13 patients unknown; ***72 patients unknown; ****14 patients unknown; *****24 patients unknown.

respectively). Cancer stage (pTNM) (n=165) showed that stage 0 was the most common (45 cases, 27%) and stage I was the second most common stage (41 cases, 25%).

Postoperative survival. Of the 189 CAC patients, 170 patients had detailed clinical data including postoperative survival with clinical detailed data. The postoperative mean follow-up period was 43.5 months (range=1.1-217.5 months). Three patients underwent postoperative chemotherapy (stage II:1, stage III:1, stage IV:1) and one patient with stage II (T4b) underwent radiotherapy. One hundred and thirty- seven patients (81%) were alive and 33 patients (19%) had deceased; 24 patients died due to cancer. Survival rate and the related risk factors were analyzed in 170 patients.

Overall survival (OS) rate. The OS rate was 74.2% at 5 years after surgery and 71.6% at 10 years after surgery (Figure 1).

The risk factors for OS, included pathological TNM stage, histological cancer type, surgical procedures (proctocolectomy or segmental resection), preoperative cancer surveillance as an indication for diagnosis, and dysplasia in the resected specimen by postoperative pathological findings.

The OS in relation to pathologic TNM stage showed that the cumulative survival at 5 years and 10 years was 100% and 100% in stage 0, 70.9% and 70.9% in stage I, 73.4% and 64.2% in stage II, 67.9% and 67.9% in stage III, and 21.5% and 0% in stage IV, respectively, with statistical significance (Figure 2). The OS in relation to histological type showed that the cumulative survival at 5 years and 10 years was 87.9% and 87.9% in well differentiated adenocarcinoma, 78.5% and 78.5% in moderately differentiated adenocarcinoma, 51.0% and 0% in poorly differentiated adenocarcinoma, and 50.7% and 0% in mucinous cell carcinoma, respectively, with statistical significance (Figure 3). The OS in relation to the surgical procedure (proctocolectomy group: HS-IPAA, stapled IPAA, total proctocolectomy with permanent ileostomy *vs*. segmental resection group) showed that the cumulative survival at 5 years and 10 years was 92.6% and 69.5% in the proctocolectomy group and 42.1% and 36.1% in the segmental resection group, respectively, with statistical significance (Figure 4). The OS in relation to preoperative cancer surveillance as the indication for diagnosis showed that the cumulative survival at 5 years and10 years was 80.5% and 80.5% in CAC patients with cancer surveillance and 65.0% and 60.0% in those without cancer surveillance, respectively with statistical significance (Figure 5). CAC patients with or without associated dysplasia did not show statistically significant differences in terms of OS (Figure 6).

Risk factors for overall survival. Among pTNM stage, histological type, type of surgical procedure (proctocolectomy group *vs*. segmental resection group), and preoperative cancer surveillance, pTNM stage and surgical procedure were statistically significant risk factors for OS using Cox regression analysis (Table III).

Effect of surgical procedures on overall survival. To evaluate the correlation between the surgical procedure and OS precisely, the survival rate in the groups of patients with proctocolectomy or segmental resection who underwent "curative cancer surgery" were compared. "Curative cancer surgery" was defined according to the Japanese classification of colorectal, appendiceal, and anal carcinoma by The Japanese Society for Cancer of the Colon and Rectum (Third English Edition, 2019) (6). The surgery with the highest radical cure degree was defined as "curability A", which is defined as no distant metastasis (M0), no residual tumor at both proximal/distal, and no radial margins (PM0, DM0 and RM0) (6).

One hundred and twenty-seven patients with curability A surgery (proctocolectomy group: 102, segmental resection

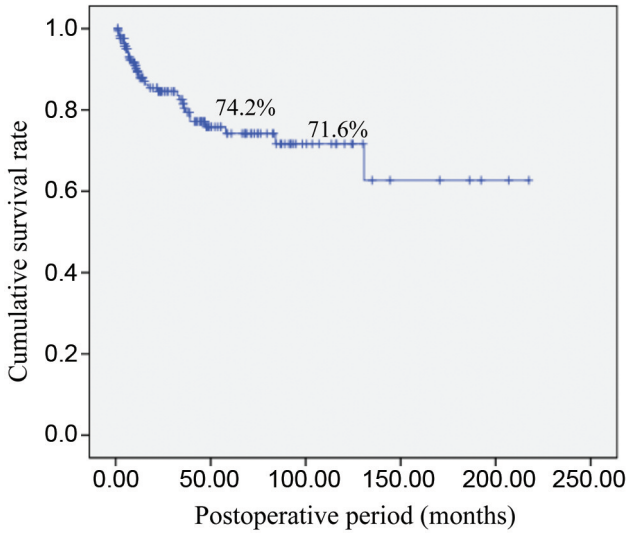

Figure 1. *Postoperative overall survival rate (n=170).*

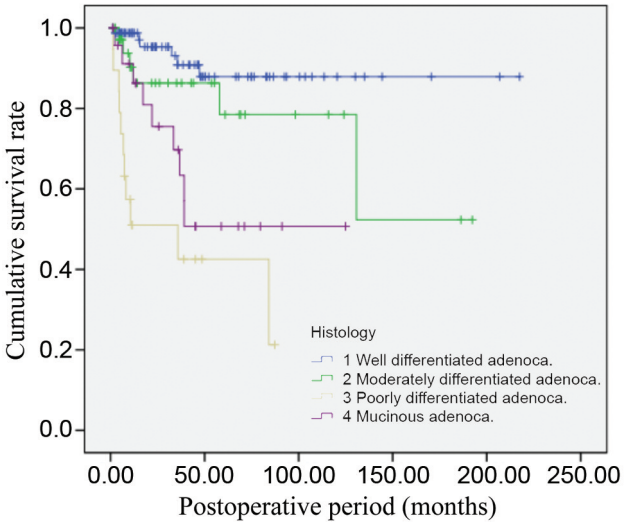

Figure 3. *Postoperative overall survival rate according to histologic type of cancer. Generalized Wilcoxon test: p=0.000, Log Rank test: p=0.000.*

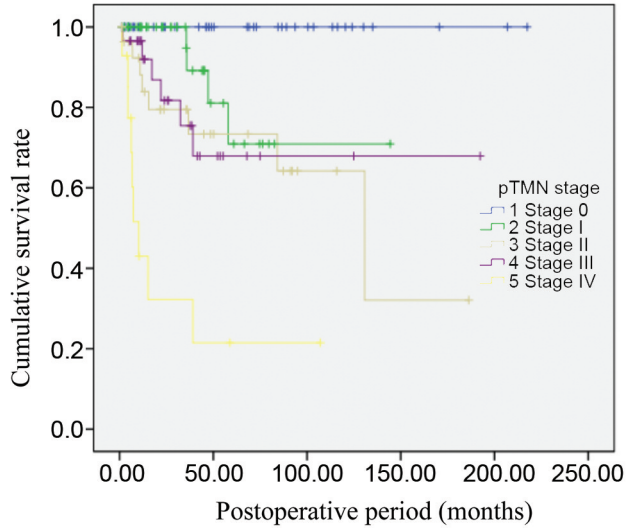

Figure 2. *Postoperative overall survival rate according to cancer stage (pTNM). Generalized Wilcoxon test: p=0.000, Log Rank test: p=0.000.*

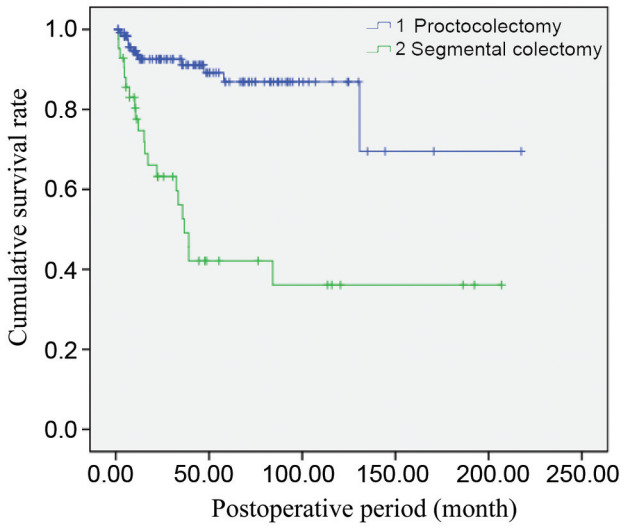

Figure 4. *Postoperative overall survival rate according to surgical procedure. Generalized Wilcoxon test: p=0.000, Log Rank test: p=0.000.*

group: 25) were included in this analysis. The cumulative survival at 5 years and 10 years was 90.3% and 90.3% in the proctocolectomy group and 69.1% and 9.2% in the segmental resection group, respectively, with statistical significance (Figure 7). The segmental resection group included significantly more patients with advanced stage cancer than the proctocolectomy group (Table IV). Based on these findings, OS was compared between both groups with stage 0, I, II, and III, separately. There was no difference in survival rate between both groups with stage, 0, I, and II. In stage III patients, the proctocolectomy group had significantly better OS than the segmental resection group (Figure 8). In the segmental resection group with stage III disease, 7 patients deceased, due to local recurrence in two, distant metastasis in two (lung metastasis in one), peritoneal dissemination in one, respiratory dysfunction in one, and uterine cancer in one.

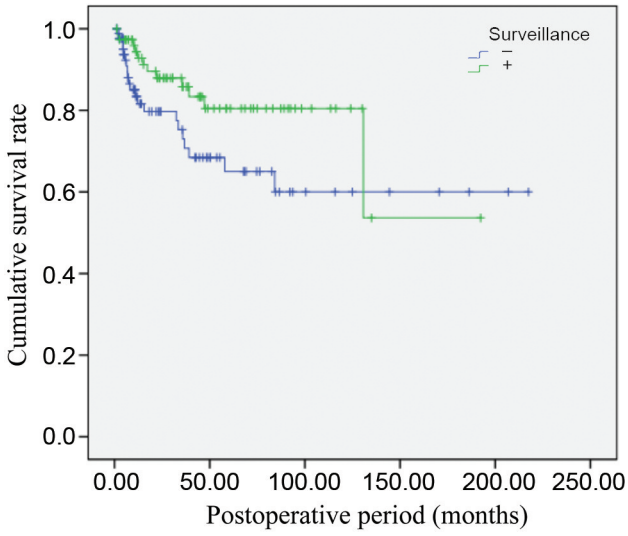

Figure 5. *Postoperative overall survival rate according to diagnosis by cancer surveillance. Generalized Wilcoxon test: p=0.043, Log Rank test: p=0.0463.*

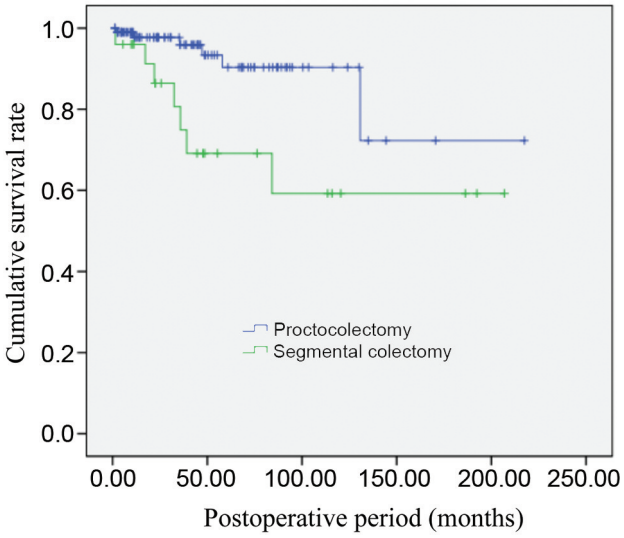

Figure 7. *Postoperative overall survival rate according to surgical procedure in patients with curability A surgery. Generalized Wilcoxon test: p=0.000, Log Rank test: p=0.000.*

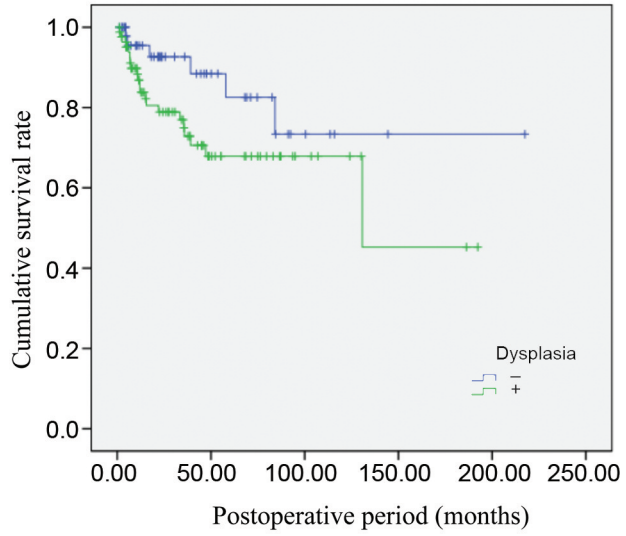

Figure 6. *Postoperative overall survival rate according to the presence of dysplasia in the resected specimen: Generalized Wilcoxon test: p=0.081, Log Rank test: p=0.057.*

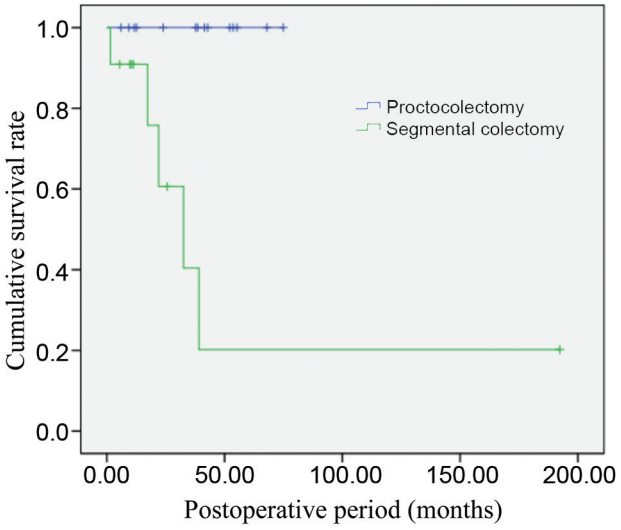

Figure 8. *Postoperative overall survival rate according to surgical procedure in stage III patients. Generalized Wilcoxon test: p=0.004, Log Rank test: p=0.001.*

Discussion

Ulcerative colitis is well known to be associated with CAC in patients with extensive colitis and a long history of UC. The data in this study were highly reliable as details of the patients with CAC, including postoperative survival, were collected directly from the authors who reported the CAC in the case report.

In this study, the most common cancer types in patients with CAC was rectal cancer and sigmoid colon cancer (52%, 18% respectively), and a higher incidence of multiple cancers (27%) and mucinous adenocarcinoma (16%) was observed compared with sporadic CRC. These findings were consistent with previous studies in Western countries (7, 8).

The distinct feature of CAC patients in this study was the inclusion of many early-stage patients (stage 0:27%, stage I: 25%, stageII:19%, stage III: 19%, stage IV: 10%). The postoperative overall survival rate was 74.2% at 5 years after surgery and 71.6% at 10 years, which was similar to that of sporadic colorectal cancer in Japan (72.1% at 5 years after surgery) (9, 10). This study probably showed the oncological characteristics of CAC treated with surgery alone because only four patients with postoperative chemotherapy or radiation were included. With regards to the postoperative survival of CAC compared with sporadic CRC, the results of previous studies were controversial. It was reported that there was no difference in the overall survival rate between CAC and sporadic cancer (11). Furthermore, no difference was found in the distribution of cancer stage and survival rate in each stage between colitic cancers and non-colitic cancers (12, 13). In two stage-matched cohort studies, there was no difference in OS between CAC patients and ordinary CRC patients (14, 15). The Danish study that included a large number of patients showed poor survival in CAC patients compared to sporadic CRC patients (16). In the Japanese study, CAC patients showed poor survival compared to sporadic CRC patients only in the advanced stage (Stage III) (17).

With regards to risk factors of postoperative OS, Cox regression analyses confirmed pathologic TNM stage and surgical procedure as prognostic factors for OS in this study.

Pathologic TNM stage as a prognostic factor suggests that the detection of early-stage cancer is one of the most important factors affecting OS.

Proctocolectomy, which can include restorative proctocolectomy or total proctocolectomy with a permanent ileostomy, is considered the optimal surgical procedure due to the multifocal malignant lesions in the large intestine in CAC patients. However, few studies have reported an improvement in OS with total proctocolectomy compared to segmental resection (4). One study in a small number of patients with CAC (17 patients) reported no cancer or high-grade dysplasia after segmental resection or total abdominal colectomy with ileorectal anastomosis (5). In our study, out of the patients that underwent curative surgery (curability A), the proctocolectomy group had better OS than the segmental resection group, and only stage III patients in the proctocolectomy group showed better survival rates compared to those in the segmental resection group. However, no death associated with cancer lesions in the remnant large intestine after segmental resection was found in the segmental resection group during follow-up in stage III patients.

The detection of early cancer or dysplasia was one of the most important factors affecting

OS after surgery in this study. Appropriate cancer surveillance by colonoscopy is thought to be the best way to achieve early detection (5, 18, 19).

Table III. *Cox regression analysis for risk factors of postoperative survival (n=170).*

Factors	HR	95%CI	*p*-Value
pTMN stage	2.48	1.63-3.77	0.00
Histological type	0.99	0.69-1.45	0.99
Type of surgical procedure	2.89	1.27-6.59	0.01
Preoperative cancer surveillance	0.71	0.32-1.60	0.416

Table IV. *Cancer stage in the patients with proctectomy, segmental colectomy.*

pTMN	Proctocolectomy (n=102)	Segmental colectomy (n=25)	*p*-Value*
Stage 0	39	5	0.006
Stage I	32	6	
Stage II	17	3	
Stage III	14	11	

*Mann Whitney *U*-test.

Recently, endoscopic resections were performed for visible dysplasia (20). However, it is imperative that the efficiency of this treatment is evaluated in terms of the possibility of an incomplete endoscopic resection and of metachronous, multifocal, invisible malignant lesions. Surgical treatment should be performed for CAC. Based on our findings and the concept of multifocal malignant lesions, the optimal surgical option should be proctocolectomy (restorative proctocolectomy or total proctocolectomy with permanent ileostomy).

This study had several limitations. First, this is a retrospective study with a relatively small number of CAC patients. Second, the data of this study were not recent, as they were obtained from studies before 2006. However, the surgical procedure itself has not changed and the postoperative survival based only on surgical treatment, without the addition of alternative treatments such as chemotherapy and radiotherapy, could be analyzed. Third, selection criteria for CAC patients with segmental colectomy were not clarified. Forth, the definition of cancer surveillance was based on each author, and may have not been completely identical among all.

Conclusion

The postoperative OS rate of CAC with UC was similar to sporadic colorectal cancer, and pathologic TNM stage and surgical procedure were confirmed as prognostic factors for OS. Based on our findings, diagnosis of cancer at an early stage is important through the recommended use of appropriate cancer surveillance colonoscopy. Also, proctocolectomy

(restorative proctocolectomy or total proctocolectomy with a permanent ileostomy) is recommended as a surgical procedure to achieve good postoperative OS.

Conflicts of Interest

The Authors have no conflicts of interest related to this study.

Authors' Contributions

Akira Sugita: study design, acquisition of data, analysis and interpretation of data, drafting the article, critical revision of the article for important intellectual content. Hiroki Ikeuchi: acquisition of data, analysis and interpretation of data, critical revision of the article for important intellectual content. Yuuji Funayama: acquisition of data, critical revision of the article for important intellectual content. Kitaro Futami: acquisition of data, critical revision of the article for important intellectual content. Tsuneo Iiai: acquisition of data, critical revision of the article for important intellectual content. Michio Itabashi: acquisition of data, critical revision of the article for important intellectual content. Yasuo Suzuki: drafting the article, critical revision of the article for important intellectual content.

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