

Relationship between Ulcerative Colitis Patients Treated with Leukocytapheresis and Ulcerative Colitis-associated Colorectal Cancer

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Abstract. *Background:* Leukocytapheresis (LCAP) is a recent modality for treatment of patients with ulcerative colitis (UC). This study aimed to assess whether LCAP changed the development of colorectal cancer (CRC) in patients with UC. *Patients and Methods:* A total of 42 patients with UC underwent surgical treatment from January 2001 until October 2010 at Kurume University Hospital. The patient details, preoperative therapy, operative indication and complications were obtained from our prospective database. Univariate, multivariate analysis and tree model were used for statistical analysis. *Results:* In patients who received LCAP before surgery, CRC was significantly less frequent ($p=0.0321$). CRC incidence following LCAP increased when the disease period from diagnosis of UC exceeded 133 months. Multivariate analysis showed that the odds for undergoing LCAP were significantly higher ($p=0.0305$) in those cases with a total dose of steroid more than 2.57 g. *Conclusion:* LCAP may suppress CRC in UC patients.

Ulcerative colitis (UC) is an inflammatory bowel disease of unknown etiology that involves severe inflammation of the colonic mucosa (1). The number of UC patients recorded in Japan in 2008 was 140,721 and is on the rise.

Patients with inflammatory bowel disease (IBD) are at increased risk of developing colorectal cancer (CRC). Eaden *et al.* (2) showed cumulative risks of 2%, 8% and 18% after 10, 20 and 30 years of disease, respectively, in patients with

UC. Thus, the longer the period of this disease, the higher is the risk of development of UC-associated CRC. IBD-associated colorectal carcinogenesis is characterized by an inflammation–dysplasia–carcinoma sequence (3) which differs from the adenoma–carcinoma sequence in sporadic CRC. High-grade or multifocal low-grade dysplasia indicates that the entire mucosal lining of the colon exposed to chronic inflammation is at increased risk of developing cancer (3, 4), thereby indicating the need for proctocolectomy.

IBD patients are advised to undergo routine colonic surveillance aimed at detection of dysplasia or asymptomatic early CRC at a surgically curable stage. Currently, the commonly followed surveillance guidelines are those defined by the American Gastroenterological Association (5) and the British Society for Gastroenterology (6). These guidelines recommend commencing surveillance after 8-10 years of disease in cases of Crohn's disease or extensive UC and after 15-20 years of disease in cases of left-sided UC. Starting surveillance before these time intervals is not recommended. However, the evidence is poorly based. Some studies have assessed the time interval between the occurrence of IBD and CRC and evaluation of how often IBD-associated CRC occurred before the first surveillance colonoscopy was advised that for patients with pan-colitis, a colonoscopy should be conducted every 3 years in the second decade of disease, every 2 years in the third decade, and yearly by the fourth decade of disease (7-9).

Leukocytapheresis (LCAP), and granulocyte and monocyte adsorption apheresis (GMA) are extracorporeal therapies for UC recently developed in Japan. These therapies reduce inflammation and promote the restoration of the intestinal mucosa by removing activated leukocytes from blood (10, 11). LCAP has shown a high response rate of 74% in steroid-refractory patients with UC (12) and its therapeutic effects are comparable to those of steroid therapy in steroid-naïve patients with UC (13).

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Table I. Clinical information regarding patients (n=42).

	Value	Range
Mean age (years)	41.6	(13-78)
BMI	20.5	(13.2-30.8)
Male:female	29:13	
Left-side:total colitis	11:31	
Chief complaint		
Bleeding	27	
Abdominal pain	12	
Diarrhea	15	
Stenosis of colon	2	
Left back pain	1	
Duration of disease (months)	97.1	(2-276)
Mean total steroid (g)	16.4	(0-80)
Preoperative mean steroid (mg/day)	15.5	(0-60)
LCAP before operation		
Yes:no	31:11	
Surgery		
Emergency:elective	9:33	
Indications for surgery		
Absolute:relative	15:27	

BMI: Body mass index; LCAP: leukocytapheresis.

This study aimed to assess the indications for LCAP and the whether LCAP changed the development of CRC in patients with UC.

Patients and Methods

Patients and tissue samples. A total of 42 patients with UC who underwent surgical treatment from January 2001 until December 2010 at Kurume University Hospital in Fukuoka were included in the study. Written informed consent from all patients and approval from The Institutional Review Committee for Research on Human Subjects, Kurume University was obtained. The clinical information regarding the patients is summarized in Table I. All patients underwent total colectomy, ileo-anal anastomosis and diverting ileostomy. Ileostomy was closed 3 to 6 months following surgery. If cancerous lesions were detected prior to surgery, oncological principles were followed during the surgical procedure.

Data collection. Data was collected from a well-maintained prospective database. We divided the patients into two groups: UC with CRC or high-grade dysplasia (CCC), and UC without CRC or high-grade dysplasia (UCC).

Data analysis. Univariate analysis was performed for age, body mass index (BMI), duration of disease, total steroid dose (g) and preoperative steroid dose (mg/day) using Wilcoxon test. Gender, with or without LCAP, type of disease, and surgical procedure were analysed using Fisher's test. We then applied the tree models by taking the response variable as CCC or UCC group and the explanatory variable as the criteria studied by univariate analysis. The tree model is a useful method which permits the automatic execution of the process of determining the factors, setting the threshold value and by differentiating the patients successively into

Table II. Comparison between groups of patients with colorectal cancer (CCC) and those without (UCC) using univariate analysis.

	CCC	UCC	P-value
Mean age (years)	45.5±18.0	40.9±18.9	0.4719
BMI	18.4±2.5	20.8±3.2	0.1178
Gender			
Male	5	23	0.6448
Female	1	13	
LCAP before surgery			
Yes	2	29	0.0321
No	4	7	
Type of disease			
Left-side	2	9	0.6432
Total colitis	4	27	
Duration of disease (month)	124.5±65.6	92.5±71.6	0.189
Mean total steroid (g)	16.9±15.6	14.6±13.3	0.7053
Mean steroid (mg/day)	13.8±13.8	15.8±14.2	0.6368
Surgery			
Open	2	12	1.0000
HALS	4	24	
Complications following surgery			
Yes	4	27	0.6437
No	2	9	

BMI: Body mass index; LCAP: leukocytapheresis; HALS: hand-assisted laparoscopic surgery.

two groups. It can deal automatically with the problem of interaction between the many explanatory variants and also permits easy interpretation of numerical and factorial variants existing side by side, and can find the hidden structures shown by the data.

Multivariate logistic analysis was carried out by taking explanatory variable as the factors selected by the tree model and by taking the response variable as the presence of CCC. Statistical analyses were performed using SAS 9.1 and JMP 7.0 (SAS Institute, Cary, NC, USA).

Results

Operative indications. There were 33 elective cases and 9 emergency cases. In the UCC group, the indications for surgery were resistance to medical therapy in 27 patients, severe colitis in 1 patient, uncontrolled bleeding in 6 patients and toxic mega colon in 2 patients. In the CCC group, indications were CRC in 5 patients and high-grade dysplasia in 1 patient.

Univariate analysis. Univariate analysis was performed by dividing the cases into two groups: CCC and UCC (Table II). The results showed that there were significantly fewer cases of cancer/dysplasia in patients who received LCAP before surgery ($p=0.0321$), but no significant differences were found in regard to other variables.

Data analysis using the tree model. We then tried to determine the factors associated with development of CRC in

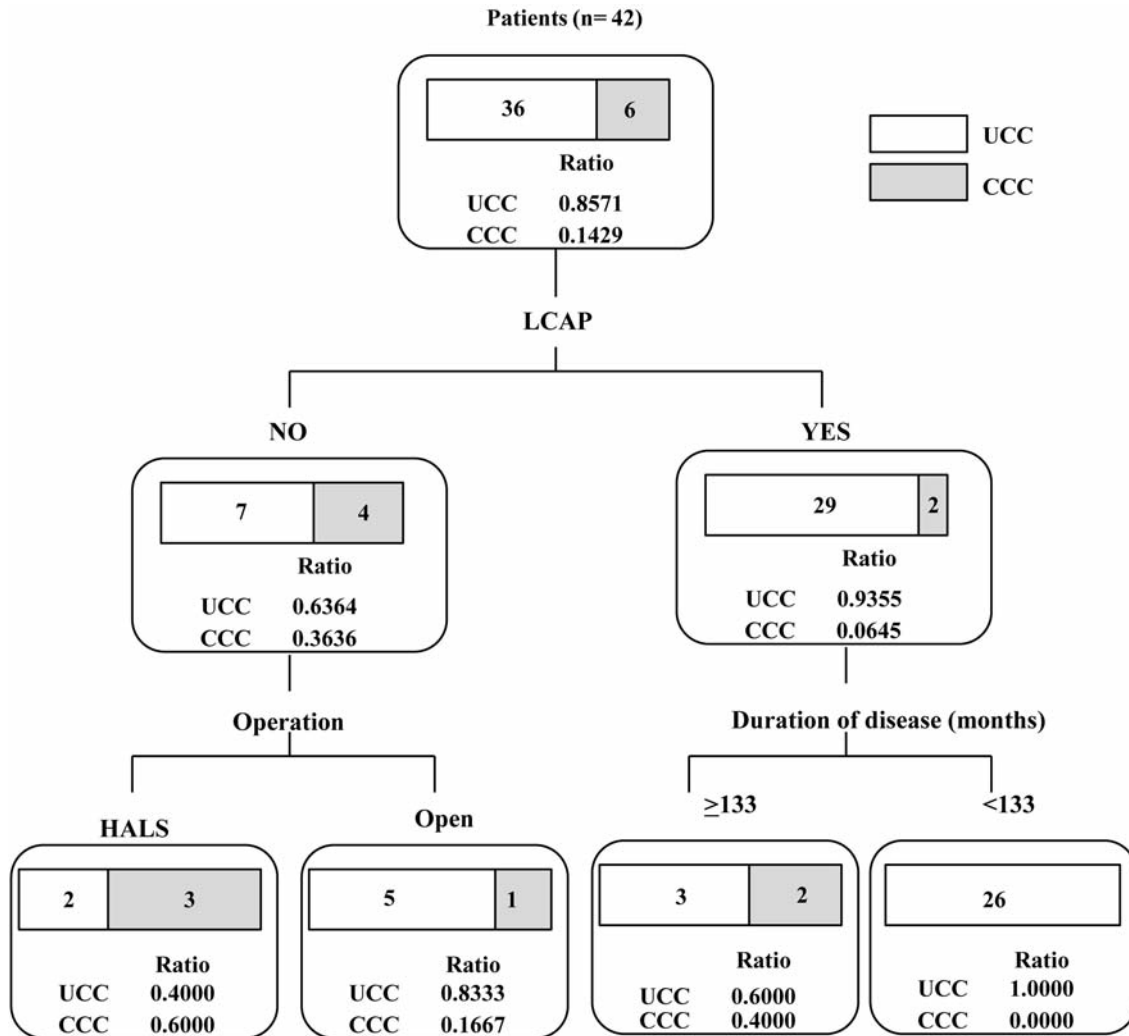


Figure 1. Analysis of data for UC patients using a tree model (n=42). The response variable is the application criterion whether or not the case was one of colorectal cancer.

patients with UC. We performed a probing analysis of the data using the tree model. The first analysis was carried out by taking the response variable as “whether or not the case had CRC” while the explanatory variable was defined in terms of “whether or not LCAP had been performed”, “duration of disease prior to surgery” and “type of surgery”. Figure 1 demonstrates that there were more cases which did not receive LCAP in the CCC group. In the CCC/LCAP group, all the cases had disease for longer than 133 months, whereas only 3 out of 29 cases of the UCC/LCAP group had a disease period longer than 133 months. This suggested that it might be possible to reduce the number of cases in the CCC group by performing LCAP and also for patients undergoing LCAP, the suspicion of CCC may increase when the disease period from diagnosis of UC exceeds 133 months.

In the second tree model, we took the response variable as “with or without LCAP” and explanatory variables as the descriptors such as “total steroid dose”, “type of surgery”, “gender” and “age” (Figure 2). This demonstrated that the majority of LCAP-treated cases belonged to the group that had a total steroid dose of 2.57 g or more. From this analysis, it can be assumed that administration of a total steroid dose of 2.57 g or more may suggest an indication for performing LCAP.

Multivariate logistic analysis. Multivariate logistic analysis was carried out based on the results obtained from the tree model (Table III). It showed that the performance of LCAP resulted in a significant decrease of the odds for CCC ($p=0.0467$). Other variables did not show a significant relation. It was also found that the odds ratio for undergoing

Table III. Multivariate logistic analysis for variables associated with ulcerative colitis-associated colorectal cancer (a) and leukocytapheresis (b).
a.

Characteristic	OR	95% CI	P-value	
LCAP	8.425	1.032-68.774	0.0467	(No vs. yes)
Operation type	2.497	0.274-22.74	0.4168	(HALS vs. open)
Duration of disease	2.853	0.37-21.989	0.3143	(≥133 months vs. <133 months)

b.

Characteristic	OR	95% CI	P-value	
Total steroid (g)	17.33	1.308-229.625	0.0305	(≥2.57 g vs. <2.57 g)
Operation type	2.343	0.453-12.115	0.3099	(HALS vs. open)
Gender	0.694	0.117-4.132	0.6884	(male vs. female)
Age	0.307	0.019-4.876	0.4024	(≤24 years vs. <24 years)

OR: Odds ratio; CI: confidence interval; LCAP: leukocytapheresis; HALS: hand-assisted laparoscopic surgery.

LCAP was significantly higher ($p=0.0305$) for those cases with a total dose of steroid more than 2.57 g. These results were similar and confirmed the outcome of the tree model.

Discussion

Our study showed that LCAP reduced the percentage of CCC in UC patients using a tree model analysis. On the other hand, when the disease period was over 133 months in the LCAP group, the percentage of CRC cases increased as shown by statistical analysis.

Consensus has already been reached on the indication of surgery for UC. In surgical management of cases with UC, the incidence of colectomy has been reported as being approximately 10% in the first year of onset, 4% in the second year and thereafter increasing by 1% each year, with 35% of the cases requiring surgical management at 5 years (14). Recent effective modalities of treatment have reduced the rate of surgery (15). Cancer and high-grade dysplasia is one of the absolute indications for surgery in UC patients, and was 15.4% in this study.

Patients with longstanding UC and Crohn's disease have an increased risk of developing CRC (2, 16-18). The mechanism behind this is not well understood. The risk appears to be related to the cumulative effect of chronic inflammation and correlates directly with the extent and duration of the disease, as well as the severity of inflammatory activity. UC is associated with the infiltration of large number of leukocytes in the bowel mucosa, which can cause extensive mucosal injury by releasing a large number of inflammatory mediators (19, 20). LCAP reduces bowel inflammation and promotes the restoration of the intestinal mucosa by removing activated leukocytes from the blood stream (10, 11). In this study, the odds ratio for undergoing LCAP was significantly higher ($p=0.0305$) for

those cases which received a total dose of steroid more than 2.57 g, this suggests that this might be an indication for performing LCAP. There was also a significant difference detected in terms of patients who underwent LCAP before surgery ($p=0.0321$), which showed that the incidence of CRC seemed to decrease in patients undergoing LCAP. This result was further confirmed by multivariate analysis.

In recent years, there have been many discussions regarding surveillance methods for discovering CRC (5, 6, 21-23) in patients with UC. Although the importance of CRC surveillance has been recognized, there are no unified standards for surveillance and biopsy. Recently, magnification endoscopic examination (24) and triage of cases with a high risk of cancer formation using gene markers (25-29) has been used aiming at further improvement in surveillance effectiveness. However, these methods have not yet been directly linked to clinical practice. Our results show that when the disease period exceeds 133 months in LCAP-treated patients, the number of CCC cases increased, which suggests that there may be an increased risk of development of CRC in LCAP-treated patients after 133 months, thus warranting careful surveillance.

We carried out probing analyses of the propensity of a case becoming a CCC using univariate analysis, tree model and multivariate analysis by logistic regression. The results suggest that it may be possible to reduce the number of CCC cases by performing LCAP and in those cases where LCAP had been performed if the disease period exceeded 133 months, this may be a risk factor for development of CRC. Furthermore, it was demonstrated that the administration of a total steroid dose of 2.57 g or more may be an indication for performing LCAP. This is an initial study suggesting the relationship between LCAP and CRC in patients with UC a small sample size; however, a larger series is needed to confirm these findings.

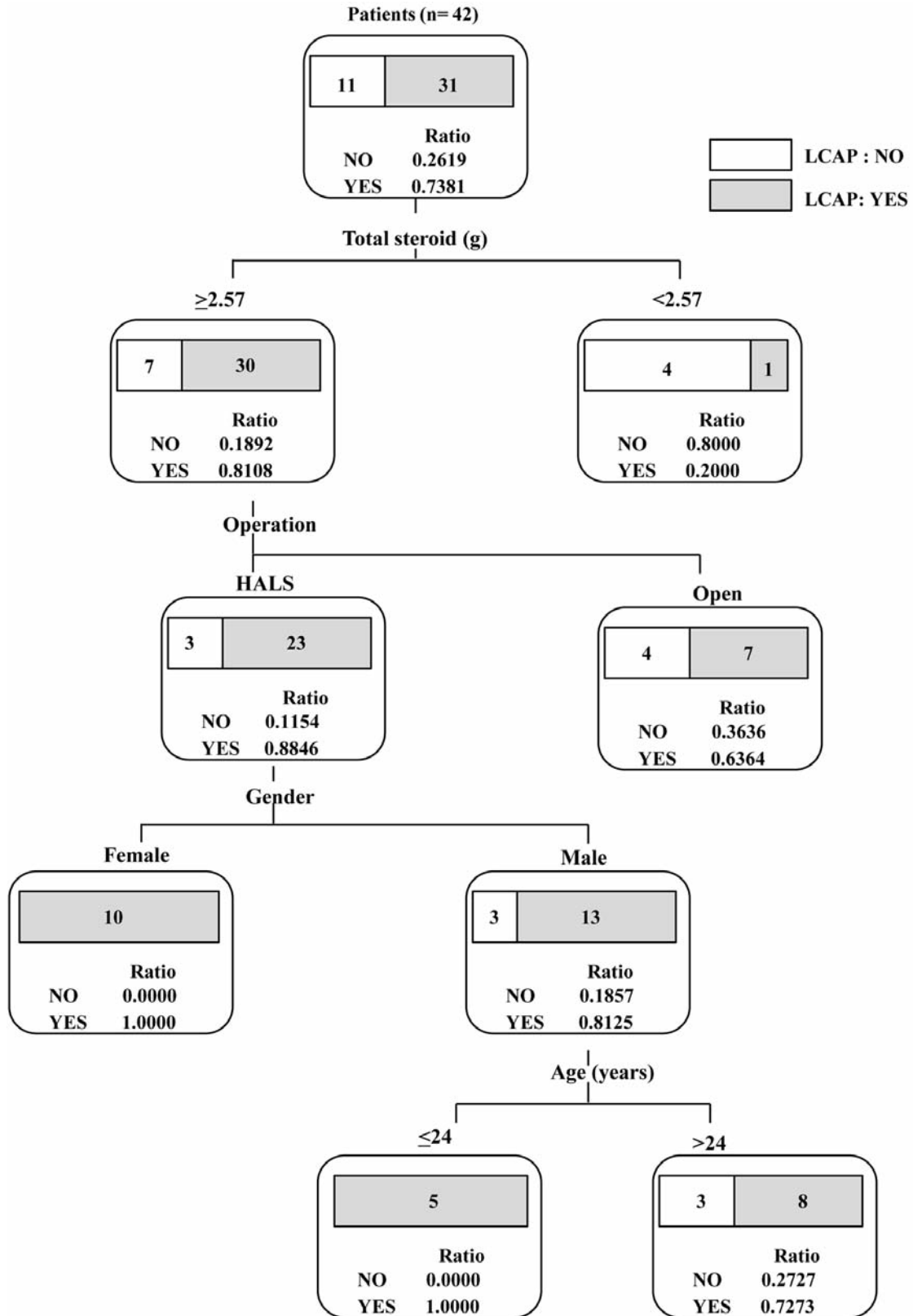


Figure 2. Analysis of data for UC patients using a tree model (n=42). The response variable is the application criterion whether or not the case underwent leukocytapheresis.

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