Clinical Course of Colorectal Cancer in Patients with Ulcerative Colitis

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Abstract. *Background: Colorectal cancer that develops as a complication of ulcerative colitis (UC) is a serious problem that affects the patient's prognosis. Such cancer is characterized by development at an early age, a high incidence of multiple tumors, poorly differentiated carcinoma and mucinous carcinoma. Special attention should therefore be paid to the diagnosis and treatment of such cancer. Patients and Methods: One hundred and seventy-four patients with UC underwent surgery in our Department between July of 1985 and December of 2009. Of these, 22 had concomitant colorectal cancer. We performed a retrospective study to investigate these patients. Result: The incidence of colorectal cancer as a complication of UC was 12.6%. The male:female ratio was 14:8, and the average age at surgery was 54.6 (32-79) years. In addition, when examining the lesion type of UC, it was revealed that the total colitis type accounted for 77.3% of colorectal cancer cases in UC patients. Regarding the site of development of colorectal cancer, 14 out of the 22 patients had cancer in the distal end. The average period from the development of UC to the diagnosis of colorectal cancer was 14.7 (0.6-40.5) years. The cumulative incidence rates over 10 and 20 years were 5.1% and 17.5%, respectively. Histologically, poorly differentiated adenocarcinoma and mucinous carcinoma were confirmed in 38.1% of the patients, and dysplasia was also confirmed in 53.8%. In addition, multiple tumors were confirmed at a rate as high as 27.3%. Cancer detection through surveillance has increased, and colorectal cancer was detected in 13 out of the 22 patients by routine surveillance. In cases where cancer was detected by surveillance colonoscopy, 46.2% of lesions were early cancer.*

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We therefore consider that surveillance is useful. However, we experienced a case that could not be diagnosed by endoscopy that was successfully diagnosed by fluoroscopy. The case was noted to have stricture. Conclusion: The cumulative incidence rates over 10 and 20 years were 5.1% and 17.5%, respectively. Since the average period from the onset of UC to the diagnosis of colorectal cancer was 14.7 years, routine surveillance examinations are necessary for patients with a history of UC of at least 10 years. In addition, patients with strictures must be examined using both colonoscopy and fluoroscopy because diagnosis with colonoscopy alone may be inadequate.

Various complications pose a problem for patients with long-standing ulcerative colitis (UC). The development of colorectal cancer is an especially serious problem that affects the patient's prognosis. The characteristics of colorectal cancer in patients with UC differ from those of general colorectal cancer. Previous reports have indicated that UC-related colorectal cancer results from chronic inflammation, and the cancer is often relatively poorly differentiated and occurs at multiple sites, conferring a poorer prognosis than general colorectal cancer.

Although early detection is always a goal, colorectal cancer resulting from such UC-related inflammation must be detected as dysplasia, evident as cancer or its precursor, before symptoms appear, allowing surgery to be performed in the early stages of disease. Periodic surveillance colonoscopies are considered an effective way of achieving these goals; however, in many of the cases investigated by this Department, the cancer was still not detected until it was in an advanced state. We herein report a detailed investigation of UC patients who underwent surgery for colorectal cancer and the clinical course of that cancer.

Patients and Methods

A total of 174 patients underwent surgical treatment for UC in this Department from July 1985 to December 2009. Among them, 22 (12.6%) patients with UC developed colorectal cancer as a complication. The male:female ratio of these cancer patients was

Table I. *Detection of colorectal cancer.*

	Symptoms	Cases, n
Symptomatic cases	Melena	5
(9 cases)	Diarrhea	2
	Anal pain	1
	Ileus (nausea, abdominal pain)	1
	Year	Cases, n
Surveillance cases,	1985-1999	2
symptom-free	2000-2004	2
(13 cases)	2005-2009	9

Table II. *Result of histological findings.*

	Symptomatic cases 8 lesions (7 cases)	Surveillance cases 13 lesions (6 cases)
Depth of tumor*		
Tis	3	5
T1	1	1
T2	1	2
T3	2	5
T4	1	0
Histological types		
Well-or moderately differentiated	6	7
Poorly differentiated, mucinous or signet-ring	2	5
Neuroendcrine	0	1
Dysplasia (53.8%)	2	5

*TNM classification.

14:8, and the average age at surgery was 54.6 (32-79) years, showing a tendency for development at an early age, compared with the average age of 64.4 years at the time of surgery for general colorectal cancer. A total of 77.3% (17/22) of these lesions were the total colitis-type, 18.2% (4/22) were of the left-side colitis type and 4.5% (1/22) were of the proctitis type.

Results

In terms of the impetus for the detection of colorectal cancer, 9 patients underwent a gastrointestinal examination as a result of exacerbated UC, and 13 patients were identified by surveillance colonoscopy. The most prevalent exacerbation of UC was in the form of melena, which 5 patients suffered. Two had increased diarrhea, 1 had anal pain, and 1 had ileal symptoms. Anal pain and ileal symptoms may be symptoms associated with the development of colorectal cancer.

Cancer detection through surveillance has increased, particularly over the last few years. In the last 5 years, cancer was detected by surveillance colonoscopy in 9 patients, indicating that 75% of the tumors detected were found as a result of surveillance colonoscopy (Table I). A diagnosis was made by this hospital's Pathology Department, and the results of the final pathological diagnosis of 21 lesions from 13 patients from whom detailed findings were obtained are shown in Table II. In cases where cancer was detected by surveillance colonoscopy, 6 lesions (46.2%) were early cancer (Tis or T1) , while 7 lesions (53.8%) were in the form of advanced cancer (T2, T3 orT4) (Table II). In order to improve patients' prognosis, it is necessary to determine ways to detect cancer in an earlier stage, including the development of new endoscopy techniques, and selection of which patients should be targeted for surveillance, and how often surveillance colonoscopy needs to be performed.

In our present series, as a result of fluoroscopy one patient with UC was diagnosed with colorectal cancer. The patient, a 34-year-old male, had suffered from UC for 14 years. The patient was under surveillance. For this patient, the examination, not every year, was carried out every 3 years,

because the course of ulcerative colitis in this patient was uneventful. Colonoscopy revealed strictures but no carcinomas; a diagnostic biopsy revealed that the strictures were group IV. Fluoroscopy depicted stricture lesions that were believed to be advanced cancer at the same sites, so surgery was performed. Localized metastatic lesions were noted in the peritoneum of this patient. A proctocolectomy and ileostomy that included the peritoneal metastases were performed. Today, 15 months postoperatively, the patient is continuing to undergo chemotherapy (Figure 1).

In terms of the site where the cancer developed, cancer developed closer to the anus than the sigmoid colon in 14 out of the 22 patients (63.6%). In addition, 6 patients (27.3%) had multiple tumors, which is a common feature of UC-related colorectal cancer (Table III).

A representative case was the finding of multiple colorectal tumors in a 42-year-old male whom we encountered. The patient had suffered from UC for 23 years. Surveillance colonoscopy revealed a disease-associated lesion or mass (DALM) in the transverse colon. Lesions were also noted in the ascending and descending colon. Ultimately, an endoscopic mucosal resection (EMR) was performed to remove the ascending colonic and colonic lesions, and examination of those specimens led to a diagnosis of well-differentiated adenocarcinoma. The postoperative pathological diagnosis of resected specimens ultimately revealed cancer at 5 sites. The patient developed liver metastases in the 20th month postoperatively and is currently undergoing chemotherapy.

Subsequently, we investigated how these patients underwent surgery. The surgical procedure performed was a total coloproctectomy in 15 cases, a total colectomy in 2 cases, a colonic resection in the form of a right

Figure 1. *Endoscopic and fluoroscopic findings of UC accompanied with stricture lesion due to colorectal cancer. A: The endoscope could not pass through due to a stricture lesion. Histology: group IV. B: The stricture lesion with an irregular surface in the descending colon.*

hemicolectomy in 1 case, a sigmoidectomy in 2 cases, and a low anterior proctectomy in 1 case. In addition, resection was not performed in 1 case due to the presence of peritoneal metastasis (Table IV).

During the postoperative course, metastasis or recurrence was noted in 6 patients, 4 of when died. In addition, 1 patient died from another form of cancer and another died postoperatively as a result of severe pneumonia (Table V).

Discussion

The most concerning complication of long-standing UC is colorectal cancer. Colorectal cancer resulting from chronic inflammation is known as colitis-associated colorectal cancer (CAC). Eaden *et al*. performed a meta-analysis of 194 studies, and they reported a prevalence of CAC in patients with UC of 3.7%, with a prevalence of CAC of 5.4% for the total colitis-type of UC alone (1). In addition, a long history of UC is known to increase the risk of CAC in patients with UC (2-7). The report by Eaden *et al*. indicated that the cumulative incidence rate of CAC was 2% for patients suffering from UC for 10 years, 8% at 20 years (Figure 2), and 18% at 30 years (1). The present study found the incidence of CAC to be 12.6%, and the cumulative incidence rate was found to be 5.1% at 10 years and 17.5% at 20 years. These rates are higher than those reported by Eaden *et al*., but this may be due to the fact that the current patients consisted only of those who underwent surgery.

Table III. *Site of colorectal cancer.*

Site	Cases, n
Ascending colon	1
Descending colon	1
Sigmoid colon	6
Rectum	7
Anal canal	1
Multiple	6

Table IV. *Surgical procedure.*

	Procedure	Cases, n
Proctocolectomy (15 cases)	APR with ileostomy	7
	IAA	2
	IACA	6
Total colectomy (2 cases)	IRA	1
	Ileostomy (no reconstruction)	1
Partial resection of large intestine (4 cases)	Right hemicolectomy	1
	Sigmoidectomy	2
	Low anterior resection of the rectum	1
Exploratory laparotomy		1

APR: Abdomonoperineal resection; IAA: ileal pouch anal anastomosis; IACA: ileal pouch anal canal anastomosis; IRA: ileorectal anastomosis.
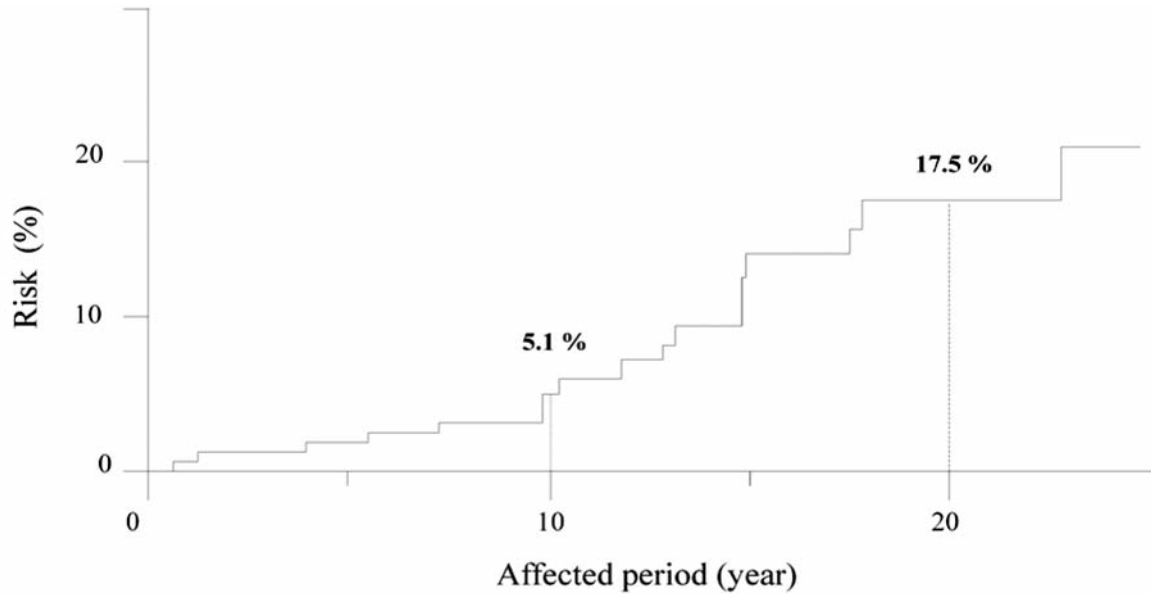
Figure 2. *Kaplan-Meier curve for the risk of colorectal cancer in UC patients.*

Table V. *Cases of recurrence.*

Case no.	Age (years)	Site of recurrence	Time from surgery to recurrence (months)	Treatment	Outcome
1	64	Lung	39	Chemotherapy	Dead
2	39	Peritoneum	Synchronous	BSC	Dead
3	79	Lung	21	Chemotherapy	Dead
4	42	Liver	20	Chemotherapy	Alive
5	46	Peritoneum	Synchronous	Chemotherapy	Dead
6	34	Peritoneum	Synchronous	Chemotherapy	Alive

BSC: Best supportive care.

The characteristics of CAC, *i.e.* the way in which it develops and its histological types, differ from those of general colorectal cancer. The manner in which colorectal cancer normally develops is known as the adenoma–carcinoma sequence. Normal mucosa is associated with the adenomatous polyposis coli (*APC*) gene, the cancer gene *K-RAS*, and the tumor suppressor gene deleted in colon cancer (*DCC*). Mutation of the tumor suppressor gene *p53* occurs and can lead to colorectal cancer. In contrast, the manner in which colorectal cancer develops in patients with UC is known as the dysplasia–carcinoma sequence. It is known that mutations in *p53* and *DCC* produce low-grade dysplasia (LGD), while activated *K-RAS* leads to high-grade dysplasia (HGD). Ultimately, these forms of dysplasia lead to colorectal cancer as a result of the dysfunction of APC (8-10).

When colorectal cancer and HGD are noted in patients with UC, surgical resection of the colon is considered necessary. However, opinions are divided with regard to LGD. In a 5-year follow-up, Goldblum *et al.* reported that LGD led to HGD, DALM or colorectal cancer in 50% of patients(11), but in a 10-year follow-up of LGD, Lim *et al.* reported that there was no association between LGD and DALM(12). In essence, no final conclusions have been reached with regard to the ultimate risk of LGD. However, it has been clearly demonstrated that the onset of CAC is closely associated with the size of lesions. Ekbom *et al.* reported that the risk of CAC was 1.7-fold higher for patients with proctitis, 2.8-fold higher for patients with left-sided colitis, and 14.8-fold higher for patients with total colitis (13). Similarly, data from the present study indicated that 17 out of the 22 patients with CAC had total colitis.

The histological types of CAC are most often poorly differentiated adenocarcinoma, mucinous carcinoma, and signet-ring cell carcinoma (14). Similarly, data from the

present study indicated that 38.1% of patients with CAC had poorly differentiated adenocarcinoma, mucinous carcinoma, or signet-ring cell carcinoma (Table II). In addition, another report has indicated that multiple tumors are more prevalent in patients with CAC, with a prevalence ranging from 8-43%, and we noted a prevalence of 27.2% in the present study (15).

The primary method of surveillance for colorectal cancer complicating UC is a blind, random biopsy of the entire colon with 2-4 specimens taken every 10 cm. However, some reports question this technique, given its cost, invasiveness and efficacy (16-18). There have been studies demonstrating the effectiveness of surveillance colonoscopy with targeted biopsies in combination with chromoendoscopy and magnifying endoscopy. Surveillance colonoscopies with targeted biopsies are being increasingly used in Japan (2, 19-23). Dysplasia is recognized in the form of a DALM, but may also be noted in the form of leaf-like projections and flat or depressed lesions, and therefore care must be taken when noting such lesions (24-26). Diagnosis using surveillance colonoscopy is difficult, and cancer is not necessarily detected in its early stages. Of the patients under surveillance by our Department, the detection rates of early and advanced cancer were about the same. Cancer was diagnosed in some patients with strictures using both colonoscopy and fluoroscopy, and the necessity for use of both colonoscopy and fluoroscopy must be considered. In addition, the tumor marker carcinoembryonic antigen (CEA) was examined in 17 patients, and carbohydrate antigen 19-9 (CA19-9) was examined in 15, but only 11.8% were positive for CEA and 20.0% were positive for CA19-9, indicating that these markers were not useful for the early detection of cancer in these patients. Biomarkers that will help with early detection therefore need to be identified.

Conclusion

UC often affects young individuals, and complications in the form of cancer are a serious problem that affect the life expectancy of these individuals. Surveillance colonoscopies are effective because they often detect cancer early, but such surveillance does not always lead to early detection. The accuracy of these colonoscopies needs to be improved, and the use of fluoroscopy should be considered. Moreover, new biomarkers must also be identified for their potential use in screening.

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