

## Study of Colorectal Cancer with Crohn's Disease

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**Abstract.** *Background:* Crohn's disease (CD) cases have been increasing and prolonged cases are now frequent. In addition, in Japan, more cases with concomitant malignant disease have also recently been reported. There is a particularly high risk of cancer occurring simultaneously in the lower rectum and the anal area. *Patients and Methods:* Two-hundred and eighty-six patients with CD had undergone surgery at this department, up to December, 2005. We studied malignant diseases concomitant with CD, based on empirical examples. *Results:* Thirteen (4.5%) were cases concomitant with malignant disease: six patients had colorectal cancer, 1 had rectal carcinoid, 1 had stomach cancer, 1 had uterine cancer, 1 had thyroid cancer, 1 had skin cancer and 2 had acute leukemia. Regarding the seven cases other than colorectal cancer, they were all juvenile patients under the age of 50, except for the stomach cancer case (69 years of age). Among the 6 cases of colorectal cancer, 5 cases were anorectal cancer and 1 was lower rectal cancer. The average age was 42.8 years (30-54 years) and the average term from CD occurrence to cancer diagnosis was 208 months (69-387 months). The one case with lower rectal cancer was intramucosal cancer which did not recur after surgery. The five cases of anorectal cancer were advanced, with invasion of the adjacent organs and 2 of them were unresectable. Four cases were of the infiltrative type, and regarding the histological findings, 4 cases were cancer with mucous production and 1 case was a poorly-differentiated endocrine tumor. Four cases had a history of anal fistula, but there was no clear causal relationship. *Conclusion:* In Japan, prolonged CD cases have been increasing and more and more cases of malignant disease with concomitant CD have been reported. There is a particularly high risk of cancer occurring simultaneously in the

lower rectum and the anal area. Therefore, careful observation, taking all appropriate diagnostic surveillance modalities into consideration, is thus believed to be important in order to achieve an early detection of such cancer.

Crohn's disease is a chronic, episodic, inflammatory condition of the bowel which may sometimes affect any part of the gastrointestinal tract from the mouth to the anus and recently Japanese patients with CD have increased in number. CD can lead to several mechanical complications within the digestive tract, including obstruction, fistulae and abscesses. Obstruction typically occurs from strictures or adhesions which narrow the lumen, blocking the passage of the intestinal contents.

CD also increases the risk of cancer in the area of chronic inflammation. For example, individuals with CD involving the small bowel are at higher risk of small intestinal cancer. Similarly, people with Crohn's colitis are at a higher risk of colorectal cancer. Siegel and Sands and Friedman *et al.* have recommended screening for colorectal cancer with colonoscopy in CD (1, 2).

### Patients and Methods

The study was carried out on 286 empirical cases of CD in which surgical treatment had been performed for intestinal lesions up to December, 2005. Not only the operational findings, but also the postoperative developments were investigated and cases with concomitant malignant disease were selected. Above all, the clinical details of cases involving concomitant colorectal cancer were closely studied.

### Results

There were 13 (4.5%) concomitant cases of malignant disorders out of the 286 cases examined. Our findings demonstrated six colorectal carcinomas (1 lower rectum and 5 anorectal area), and seven others (Table I). Excluding colorectal cancer, the patients fell into the younger category, under the age of 50, except for the stomach cancer patient

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*Key Words:* Crohn's disease, colorectal cancer, risk of cancer.

Table I. CD cases with malignant disease.

Incidence 4.5% (13/286, cases of intestinal tract surgery)	
Site	No. pts (Age gender)
Colorectal cancer	6 (see Table II)
Rectal carcinoid	1 (30 M)
Gastric cancer	1 (69 M)
Uterine cancer	1 (49 F)
Thyroid cancer	1 (36 M)
Skin cancer	1 (40 M)
Acute leukemia	2 (39 M) (44 M)

Table II. CD cases with colorectal cancer.

Incidence	6/286 (2.1%)	
Gender	Male 3/206 (1.5%)	Female 3/80 (3.8%)
Age at diagnosis of cancer (years)	42.8±10.1 (30 ~ 54)	
Affected period (development → diagnosis of cancer)	208.8±107.9 months (69 ~ 387)	
Disease type of CD	Small intestine type 1	1/106 (0.9%)
	Small and large intestine type 4	4/163 (2.5%)
	Large intestine type 1	1/17 (5.9%)

Table III. Surgical history and symptoms until the diagnosis of cancer.

Case	History of intestinal surgery	History of anal fistula	Cancer-related symptoms	Time to diagnosis of cancer from initial symptoms (months)
1	(+)	(+)	Palpable tumor, pain, hemorrhage	12
2	(+)	(+)	General fatigue	7
3	(-)	(-)	-	Regular examination**
4	(+)*	(-)	Anal fluid discharge ↑, pain	4
5	(+)	(+)	Pain, fever	21
6	(-)	(+)	Pain, dyschezia	2

\*Establishment of stoma. \*\*Case 3 is a patient who was diagnosed with ulcerative colitis and received regular examinations. The patient underwent close examination when colorectal cancer was detected and was diagnosed with Crohn's disease.

(69 years old). Among the six cases of colon cancer, five were cases with concomitant cancer of the anal area (Table II).

As for the cancer-related symptoms, four patients had anal pain and for patients with anorectal cancer, anal pain is considered an important complaint. In three of these cases it took 6 months or longer from the time at which cancer indicative symptoms were observed (21 months in 1 case) until the diagnosis of cancer was reached. Four out of the five anorectal cancer cases had a history of anal fistula (Table III).

Five cases demonstrated highly advanced cancer in which invasion of adjacent organs was detected at cancer diagnosis and two cases were unresectable. Microscopically, one case was type 2 and four cases were either type 3 or 4. Histologically, four cases were glandular cancer with mucus production and one case was a poorly-differentiated endocrine tumor (Table IV).

One patient had intramucosal cancer of the lower rectum and there was no recurrence after the operation, but CD of the anastomosis site recurred and a further operation was needed. An unfavorable prognosis could not be ruled out. Three cases of surgical removal resulted in death at 18, 17 or 3 months from cancer recurrence. One case of non-removal resulted in death within 4 months while another patient continued to receive chemotherapy and radiation therapy 9 months after the diagnosis (Table V).

The incidence of colorectal cancer during each of the individual affected periods was 2.2% from 60 months to less than 120 months, 3.1% from 120 months to less than 180 months, and 3.4% for more than 240 months (Table VI).

### Discussion

In Japan, many cases of malignant disease with concomitant CD have been reported and, according to the documentation from 2000 to 2006, have increased due to an increase in cases with a long-term course. Among the malignant diseases, 48 cases (84.2%) involved cancer of the small or large intestine (3-10) (Table VII).

On average, cancer of the small or large intestine was detected at the age of 41.8 years when CD had been present for a 15-year period. Low rectal and anorectal cancer accounted for 72.9% of the cases, while cancer with a low level of differentiation accounted for approximately 60% of the cases (3-10) (Table VIII). The risk of cancer complications in CD is considered to be higher in the lower digestive tract. According to Jess *et al.*, the standardized incidence ratio of colorectal cancer in CD varied from 0.9 to 2.2 (11-18). In the present study, the incidences of malignant disease and colorectal cancer as a complication of CD were 4.5% and 2.1%, respectively.

Table IV. Clinical pathological findings of CD cases with colorectal cancer.

Case	Site	Microscopic type	Tissue type	Progress	Dysplasia	Granuloma
<b>Resection</b>						
1	RbPE	Type 2 (Ulcerated type with clear margin)	Highly – poorly differentiated mucus (+)	ai (vagina)	(–)	(–)
2	RbPE	Type 3 (Ulcerated type with infiltration)	Mucus cancer	ai (uterus, vagina)	(–)	(+)
3	Rb	IIa (Superficial elevated type)	Highly differentiated	m	(–)	(–)
4	RbP	Type 4 (Diffusely infiltrating type)	Mucus cancer	ai (bladder, seminal capsule, prostate gland)	(–)	(–)
<b>Non-resection</b>						
5	PRbE	Type 3 or 4	Mucus cancer	ai	–	–
6	PRbE	Type 3 or 4	Poorly differentiated endocarcinoma	ai	–	–

Rb: lower rectum. P: proctos. E: external skin. ai: direct tumor invasion of other organs or structures.

Table V. Surgical outcome of CD cases with colorectal cancer.

Case	TNM classification	Treatment	Outcome
1	IIIC (T4, N2)	APR uterine apoplexy, radiation chemical therapy	18 months (Death due to redevelopment)
2	IIIC (T4, N2)	APR uterine apoplexy, radiation chemical therapy	17 months (Death due to redevelopment)
3	0 (Tis, N0)	LAR	184 months* (Alive)
4	IIIC (T4, N2)	TPE, radiation chemical therapy	3 months (Death due to redevelopment)
5	IV (Para-aortic LN)	Stoma, BSC	4 months (Death)
6	IIIC or higher	Stoma, chemical therapy radiation	9 months (Under treatment)

LN: lymph node. APR: abdominoperineal resection of the rectum. TPE: total pelvic exenteration LAR: low anterior resection of the rectum. BSC: best supportive care. Tis: carcinoma *in situ*. \*54 months, ARP at stomal-vaginal fistula.

Table VI. Risk of colorectal cancer in patients with CD.

Affected period (months)	Cases	Case of colorectal cancer (risk)
0 ~ 59	10	
60 ~ 119	45	1 (2.2%)
120 ~ 179	64	2 (3.1%)
180 ~ 239	79	
240 ~	88	3 (3.4%)

Several reports have shown that the cumulative risk of colorectal cancer as a result of complications of CD could be 1.5-5.3% (19, 20). In this study, the cumulative risk for colorectal cancer that may have a causal relationship with CD was 2.8% after 10 years.

The anorectal area was the most frequent site of cancer concomitant with CD and it was observed to occur as the infiltrative type. Cancer associated with mucus production was frequently observed which resulted in an unfavorable prognosis, several reports have shown similar results (21, 22).

Table VII. Fifty-seven cases of malignant disease that developed as a complication of CD.

Reported cases in Japan from 2000-2006			
Site	Cases	Site	Cases
Ileum	7 (12.3%)	Stomach	2 (3.5%)
Cecum	1 (1.8)	Ovary	1 (1.8)
Descending colon	1 (1.8)	Kidney	1 (1.8)
Sigmoid colon	3 (5.3)	Bladder	1 (1.8)
Upper rectum	1 (1.8)	Skin	2 (3.5)
Lower rectum/anus	16 (28.1)	Malignant lymphoma	1 (1.8)
Anal fistula	19 (28.1)	Abdominal desmoid tumor	1 (1.8)

In cases of anal cancer with concomitant CD, the likelihood that it has already become advanced should be considered when the symptoms are first recognized. The length of time required to make a diagnosis of cancer following the development of indicative symptoms is a serious problem (13). For anorectal carcinomas in particular, ocular inspection and manipulation can be performed, and CT and MRI examinations are effective.

Table VIII. Cases to CD with small intestine and colorectal cancer.

Site	Ileum	Colon/upper rectu	Lower rectum/anus	Anal fistula	Total or average
Gender (M/F)	3/4	5/1	10/6	13/6	31/17
Age at cancer diagnosis (years)	50.0	45.0	37.7	41.1	41.8
Affected period (months)	202.8	45.0	193.2	234.2	189.8
Type of histology					
well-differentiated	2	4	4		10 (27.0%)
moderately-differentiated	2	2	1		5 (13.5)
poorly-differentiated			2		2 (5.4)
sig	1		1	2	4 (10.8)
muc	1		6	9	16 (43.2)

The risk of cancer complications in CD is considered to be higher in the lower digestive tract and regular follow-up is therefore important.

Furthermore, it is important to conduct examinations, such as cytological assessment of discharge, taking the possibility of cancer into consideration. In the future, the establishment of a surveillance protocol for cancer complications is therefore desirable.

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