

Colorectal Adenocarcinoma in Crohn's Disease

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Objective

The authors' aim was to review the clinical features and estimate the long-term survival of patients with colorectal carcinoma complicating Crohn's disease.

Summary Background Data

Recent studies have demonstrated a significantly increased risk of colorectal carcinoma in patients with Crohn's disease.

Methods

The authors reviewed retrospectively the medical records of 30 patients with Crohn's disease admitted to The Mount Sinai Hospital between 1960 and 1989 in whom colorectal adenocarcinoma developed. All patients were operated on and follow-up was complete for all patients to 10 years after operation, to the time of death, or to the closing date of the study in December 1989.

Results

The 30 patients in this series had 33 colorectal adenocarcinomas; three patients (10%) presented with two synchronous cancers. The patients were relatively young (mean age, 53 years) and had long-standing Crohn's disease (duration >20 years in 87%). The 5-year actuarial survival was 44% for the overall series: 100% for stage A, 86% for stage B, 60% for stage C. All five patients with excluded bowel tumor died of large bowel cancer within 2.4 years; by contrast, the actuarial 5-year survival for patients with in-continuity tumors was 56%.

Conclusions

The incidence, characteristics, and prognosis of colorectal carcinoma complicating Crohn's disease are similar to the features of cancer in ulcerative colitis, including young age, multiple neoplasms, long duration of disease, and greater than a 50% 5-year survival rate (without excluded loops). These observations suggest the advisability of surveillance programs for Crohn's disease of the colon similar to those for ulcerative colitis of comparable duration and extent.

Colorectal cancer occurring in ulcerative colitis was described in 1925 by Crohn,¹ but not until 23 years later did Warren and Sommers report the first case of adenocarcinoma complicating regional enteritis.² For the next 30 years, an increasing frequency of reports of single³⁻⁵ and even multiple cases⁵⁻¹⁰ failed to dispel the skepticism surrounding this association. More recent studies have clearly demonstrated the increased risk of colorectal cancer for patients with Crohn's disease who have had extensive, long-standing, unresected colonic involvement.¹¹⁻¹⁴ In the current study, we reviewed the clinical features and estimated the long-term survival of 30 patients with colorectal carcinoma complicating Crohn's disease.

METHODS

We reviewed retrospectively the medical records of 30 patients with Crohn's disease admitted or readmitted to the Mount Sinai Hospital between 1960 and 1989 in whom colorectal adenocarcinoma developed. These patients were obtained from two sources: 21 of them were chosen from among 1695 patients with Crohn's disease who were admitted to our hospital between 1960 and 1985, whose data are kept in the computer files of our hospital. The remaining nine patients were obtained from the discharge records of our institution up to December 1989 by matching International Classification of Diseases (ICDA) codes for Crohn's disease and colorectal cancer. Nine of these 30 patients have been reported on previously,¹⁵⁻¹⁷ 3 with cancer in excluded loops and 6 with in-continuity tumors. The diagnosis of Crohn's disease was based on established clinical, radiologic, endoscopic, and pathologic criteria.¹⁸⁻²² Differentiation from ulcerative colitis was made in all cases by one or more of the following criteria: deep transverse fissure formation or fistulization; asymmetrical mucosal involvement; aggregated inflammatory pattern; confluent linear ulceration; discontinuity or segmental disease; right-sided involvement; small-bowel disease; rectal sparing; noncaseating epithelioid granulomas of the bowel or lymph nodes; and transmural inflammation.

The diagnosis of cancer was based on histopathologic findings, which were available in all cases. Patients with small-bowel cancers or colorectal tumors other than adenocarcinomas were excluded from the current study. Patients were staged by means of the modified Dukes' classification²³ as follows: A, tumor limited to the bowel wall; B, extension of tumor to mesenteric fat but no me-

tastases in regional lymph nodes; C, metastases in regional lymph nodes; and D, distant metastases.

Onset of disease was defined as time of first onset of symptoms. Follow-up information was obtained by review of hospital or tumor registry records, by contacting the referring physician, or by direct patient interview. Follow-up was completed for all patients to 10 years after operation, to the time of death, or to the closing date of the study (December 1989).

All statistical calculations were performed with the BMDP 1L²⁴ computer program. Survival analysis was calculated with the Kaplan-Meier method.²⁵ Postoperative survival curves were compared with the generalized Wilcoxon test²⁶ and the Mantel-Cox log-rank test.²⁷ Four patients who died of causes unrelated to large-bowel carcinoma were censored, and two patients who died postoperatively were included in the analysis as deaths. The differences in means were calculated by means of the two-tailed t test for unpaired data. Differences were considered to be significant when the probability value was less than 0.05.

RESULTS

Thirty patients admitted to The Mount Sinai Hospital with Crohn's disease between 1960 and 1989 developed 33 adenocarcinomas of the large bowel; three of the patients presented with two synchronous cancers (Table 1). There was a preponderance of male patients (ratio, 21 males:9 females). The mean ages at onset of Crohn's disease and at diagnosis of cancer were 32 and 53, respectively, yielding a mean duration of disease of 20 years (Table 1). Four patients presented with cancer in their first decade of Crohn's disease. Ten developed it in the second decade, nine in the third, six in the fourth, and one in the fifth. The four patients with first-decade cancer experienced onset of Crohn's disease when they were more than 60 years old (range, 61-72 years; mean, 66 years), with disease durations of 7, 2, 0, and 0 years; two patients with disease onset at 68 and 72 years had cancer and Crohn's disease diagnosed simultaneously.

Fifteen patients (50%) had ileocolitis; eight (27%), colitis; and seven (23%), ileitis only. There were no statistically significant differences among these three anatomically defined groups for mean age at onset of Crohn's disease (26.9 years, 37.9 years, and 36.1 years, respectively), mean age at diagnosis of cancer (48.8 years, 56.5 years, and 56.7 years, respectively), or mean disease duration until cancer development (21.9 years, 18.6 years, and 17.7 years, respectively).

Five patients (17%) had six tumors in excluded bowel, and the remaining 25 patients had 27 cancers in continuity. There were no statistically significant differences between the two groups for mean age at onset of Crohn's disease (27

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Table 1. SUMMARY OF CLINICAL DATA ON 30 PATIENTS WITH LARGE BOWEL CANCER COMPLICATING CROHN'S DISEASE

Patient No.	Sex	Age at CD Diagnosis (yr)	Age at Cancer Diagnosis (yrs)	DD (yr)	Follow-up (mo)	Outcome	Cause of Death	Site of Cancer	Stage	Excluded Bowel
New cases										
Ileocolitis										
1	M	10	36	26	122	Alive	—	AC	B	No
2	M	27	37	10	2	Dead	LB cancer	AC	D	No
3	F	51	69	18	0.5	Dead	Postoperative sepsis	C	D	No
4	M	36	54	18	17	Dead	LB cancer	R	C	No
5	M	22	47	25	11	Dead	LB cancer	R	C	Yes
6	F	36	72	36	89	Alive	—	S	A	No
7	F	40	71	31	15	Dead	Other	R	B	No
8	M	16	32	16	8	Dead	LB cancer	S	D	No
9	M	16	36	20	26	Alive	—	S	C	No
10	M	23	45	22	13	Dead	LB cancer	R	B	Yes
11	F	8	21	13	13	Alive	—	S	B	No
12	M	28	50	22	9	Alive	—	R	B	No
Granulomatous colitis										
13	M	56	70	14	92	Dead	Other	AC	B	No
14	M	23	39	16	9	Dead	LB cancer	RS	D	No
15	F	8	45	37	13	Dead	LB cancer	S(2)*	D	No
16	M	63	70	7	36	Dead	Other	TC	B	No
17	F	56	67	11	0.5	Dead	Postoperative sepsis	TC	D	No
18	M	20	40	20	36	Alive	—	R	A	No
19	M	9	53	44	9	Alive	—	R	C	No
Regional enteritis										
20	M	27	78	31	36	Alive	—	DC	C	No
21	M	16	38	22	2	Dead	LB cancer	RS	D	No
Cases previously reported										
Ileocolitis										
22	M	20	46	26	28	Dead	LB cancer	C	D	Yes
23	M	40	55	15	18	Dead	LB cancer	RS	D	Yes
24	M	30	61	31	10	Dead	LB cancer	C/AC*	D	Yes
Granulomatous colitis										
25	M	68	68	0	163	Dead	Other	TC	B	No
Regional enteritis										
26	F	61	63	2	385	Alive	—	TC	A	No
27	F	40	70	30	14	Dead	LB cancer	C	D	No
28	F	72	72	0	122	Alive	—	AC	B	No
29	M	17	42	25	13	Dead	LB cancer	R(2)*	D	No
30	M	20	34	14	58	Alive	—	R	C	No
		Mean (all)	32	53	20	47				

CD = Crohn's disease; DD = duration of Crohn's disease; C = cecum; AC = ascending colon; TC = transverse colon; DC = descending colon; S = sigmoid; RS = rectosigmoid; R = rectum; LB = large bowel.

* Patients with two synchronous carcinomas.

There were two postoperative deaths due to sepsis in advanced stage D cancers.

vs. 33 years), age at onset of cancer (51 vs. 53 years), and disease duration until cancer development (24 vs. 19 years).

All patients were operated on. Sixteen underwent curative surgery, eight had palliative resection, four had diversion, one had bypass surgery, and one underwent biopsy. There were two postoperative deaths; both patients had stage D tumor and died of sepsis.

Obstruction was the most common indication for surgery, occurring in 13 (43%) patients. Of the remaining 17 patients, 6 were operated on for intractable Crohn's disease, 5 for gastrointestinal bleeding, 2 for intestinal perforation with peritonitis, 2 for biopsy-proven carcinoma located in a polyp, 1 for strictures, and 1 for ileovesicular fistula. The diagnosis of cancer was made before

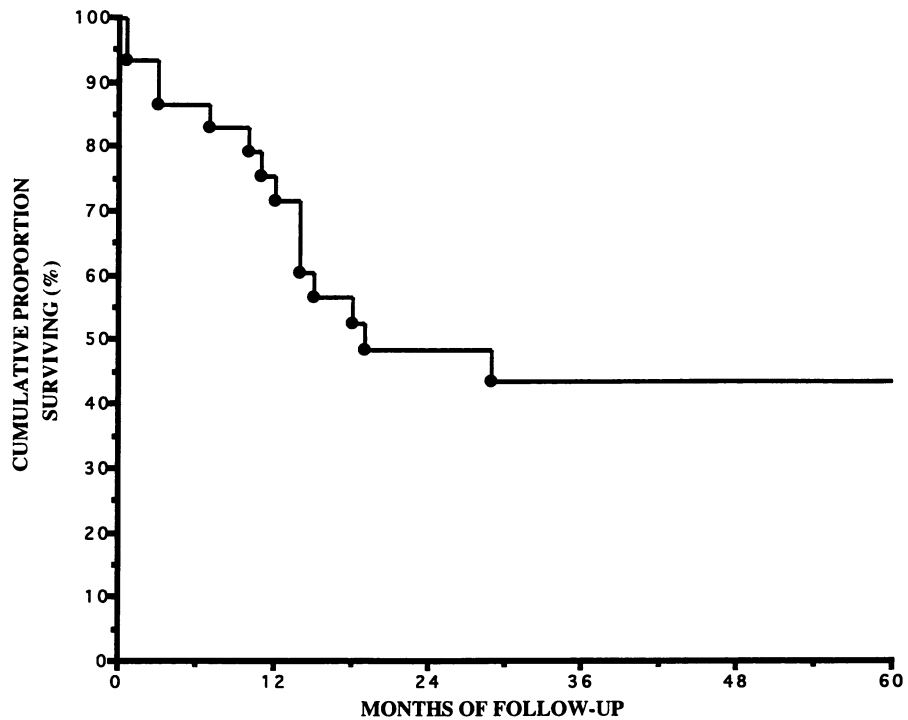


Figure 1. Survival curve calculated by the Kaplan-Meier method for all 30 patients with colorectal carcinoma complicating Crohn's disease.

MONTHS OF FOLLOW-UP	0	0.5	3	7	10	11	12	14	15	18	19	24	29	36	48	60
* NO OF CANCER DEATHS	0	2	2	1	1	1	1	3	1	1	1	0	1	0	0	0
NO OF PATIENTS AT RISK	30	30	28	24	22	21	20	19	16	14	13	11	10	9	7	6

surgery in only 16 (53%) patients (7 by colonoscopy, 5 by sigmoidoscopy, and 4 by barium enema). The cancer was diagnosed at the operating table in five (17%) patients. In the remaining nine patients (30%), the diagnosis of cancer was made by the pathologist only.

Twenty-four cancers (73%) occurred distal to the splenic flexure and nine (27%) proximal. Nineteen cancers (58%) occurred in areas of active Crohn's disease, but 14 (42%) were located in areas of the colon that were not grossly diseased, including 7 cases of colon cancer in patients whose Crohn's disease was macroscopically limited to the small bowel. Four patients (13%) presented with associated carcinomatous fistulas. Of these fistulas, two were internal (one from ascending colon to cecum, one rectovesicular), one external (from rectum), and one perianal.

Pathologic staging was as follows: three patients had stage A tumors; nine, stage B; six, stage C; and 12, stage D. Five of the 12 patients with early cancers (stages A and B) died, but only one of them died of large-bowel cancer (1 year after surgery); the other four deaths were from unrelated causes. Fourteen of the 18 patients with Duke's stage C and D cancers died, all of colorectal cancer. Of the four surviving patients, all with stage C can-

cer, one with recurrent cancer was alive at 4 years' follow-up. The other three patients were cancer free at 3 years, 2 years, and 9 months after surgery. Four of the five patients with cancer in excluded bowel had advanced tumors (one patient, stage C; three patients, stage D) and one had an early stage tumor (stage B); all five patients died.

The mean follow-up for all 30 patients after diagnosis of cancer was 47 months (median, 17 months; range, 15 days to 32 years). Fifteen patients died of large-bowel cancer (two patients with stage D disease died after surgery), with a mean survival of 11 months (range, 15 days to 2.4 years). Among these patients were five whose cancer was located in the excluded bowel, all of whom died within 10 months to 2.4 years (mean, 1.3 years). Eleven patients were still alive at the closing date of the study, with a mean follow-up of 6.9 years (range, 9 months to 32 years). Six patients survived more than 7 years (mean, 13 years; range, 7-31 years) free of colorectal cancer.

The 5-year survival rate for the 30 patients at 60 months was 44% (Fig. 1). In contrast to those with cancer in the excluded bowel, all of whom died within 2.4 years, the patients with in-continuity tumor had a 56% survival at 5 years (Fig. 2). The 5-year survival for each stage was

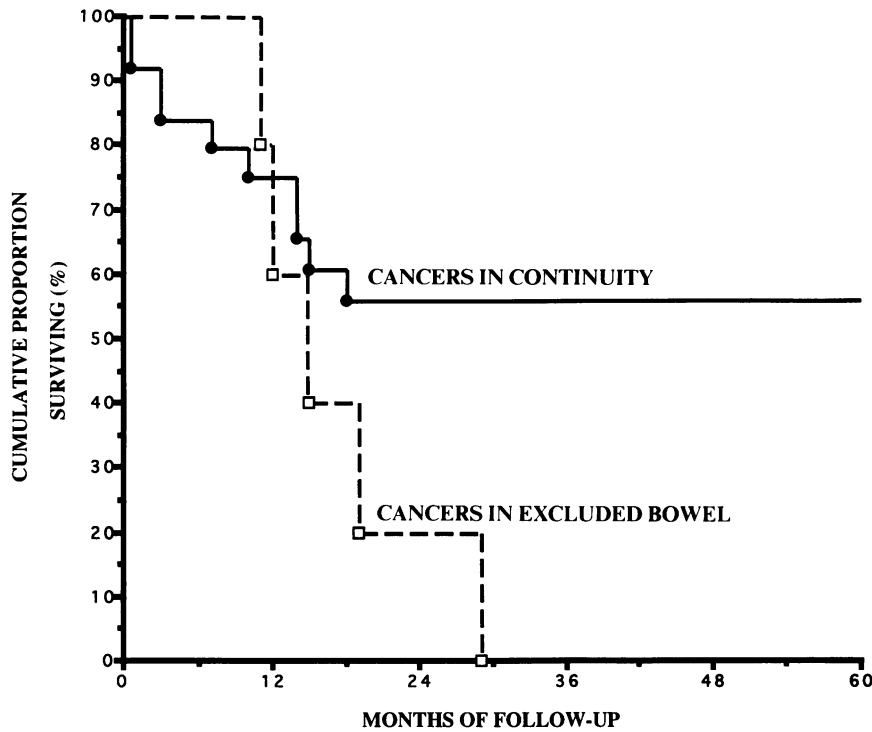


Figure 2. Survival curves for the five patients with cancer in excluded bowel and for the 25 patients with incontinuity cancer. The sample sizes were too small to be statistically significant.

MONTHS OF FOLLOW-UP	0	0.5	3	7	10	11	12	14	15	18	19	24	29	36	48	60
CANCERS IN CONTINUITY	* 0/25	2/25	2/23	1/19	1/17	0/16	0/16	2/16	1/14	1/12	0/11	0/10	0/10	0/9	0/7	0/6
CANCER IN EXCLUDED BOWEL	0/5	0/5	0/5	0/5	0/5	1/5	1/4	1/3	0/2	0/2	1/2	0/1	1/1			
* NO OF CANCER DEATHS / NO OF PATIENTS AT RISK																

as follows: A, 100%; B, 86%; C, 60%; D, 0% (all 12 of these patients died within 29 months) (Fig. 3). There was a significant difference in survival between patients with early (stages A and B) and late (stages C and D) cancers (general Wilcoxon < 0.001, Mantel-Cox < 0.001).

DISCUSSION

Thirty patients with Crohn's disease in whom large-bowel adenocarcinoma developed who were admitted to The Mount Sinai Hospital between 1960 and 1989 were reviewed retrospectively. Our data confirm previous reports^{28,29} in the following respects: a predominance of males, cancer development at an young age, a long duration of disease, a left-sided preponderance of tumors, a substantial number of patients with tumor in excluded bowel, and a considerable proportion (10%) of synchronous tumors.

The association between Crohn's disease and colorectal cancer has been controversial. Although there are now 128 patients¹⁰ in whom cancer of the large bowel has been re-

ported in association with Crohn's colitis, ileocolitis, or regional enteritis, several population-based studies have disputed the validity of the connection between these two diseases.³⁰⁻³⁴ However, all of these population-based studies calculated relative risks without regard to the populations actually at risk; namely, patients with extensive, long-standing, unresected colon disease. In fact, a recent study from Birmingham compared the cancer risk between two hospital-referred but identically selected cohorts of patients with extensive ulcerative colitis and equally extensive Crohn's colitis.¹⁴ This study established a virtually identical absolute cumulative frequency of 7% and 8%, respectively, for Crohn's disease and ulcerative colitis at 20 years, thereby confirming the previously noted similarities between cancer incidences in these two diseases.^{11-13,35}

The possible association of colorectal carcinoma with small-bowel Crohn's disease remains unknown.^{19,31,36,37} Seven (23%) of our patients, five of whom were from an earlier study,¹⁹ had overt Crohn's disease confined to the small bowel, yet carcinomas of the colon (n = 5) and rectum (n = 3, one patient having two cancers) developed. It

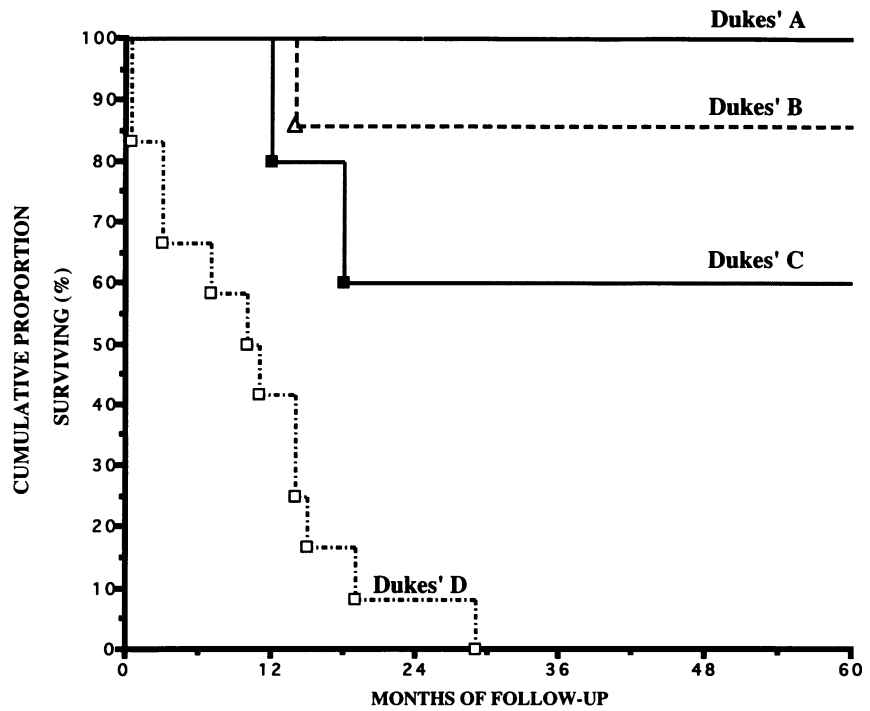


Figure 3. Survival curves according to the modified Dukes' classification. There was a statistically significant difference between early (stages A and B) and late (stages C and D) stages (general Wilcoxon < 0.001, Mantel-Cox < 0.001).

	0	0.5	3	7	10	11	12	14	15	18	19	24	29	36	48	60
STAGE A	* 0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/3	0/2	0/2
STAGE B	0/9	0/9	0/9	0/8	0/7	0/7	0/7	1/7	0/6	0/5	0/5	0/5	0/5	0/5	0/4	0/4
STAGE C	0/6	0/6	0/6	0/6	0/6	0/6	1/5	0/4	0/4	1/4	0/3	0/2	0/2	0/2	0/1	0/1
STAGE D	0/12	2/12	2/10	1/8	1/7	1/6	0/5	2/5	1/3	0/2	1/2	0/1	1/1			

* NO OF CANCER DEATHS
NO OF PATIENTS AT RISK

could be argued that colorectal cancer, a common disease, developed coincidentally in these patients, especially in the four patients older than 60 years of age at the time of cancer diagnosis. However, three of the seven patients with ileitis presented with colorectal cancers at ages 34, 38, and 42, possibly suggesting a true increase in risk. Moreover, there were no significant differences in age at onset of Crohn's disease, age at cancer development, and duration of disease related to cancer between patients with ileitis and those with ileocolitis or colitis. Finally, one of the patients with ileitis had two synchronous carcinomas, a phenomenon which occurs much more commonly among patients with inflammatory bowel disease than among the general population.³⁸⁻⁴⁰ These findings again raise the question of whether even small-bowel Crohn's disease may predispose the patient to colorectal adenocarcinoma,^{17,31,36,37} which would be consistent with the panenteric nature of this disease.

Regarding the influence of age on the development of colorectal cancer in Crohn's disease, two subpopulations should be considered. The first and larger group (26 of the 30 patients in our series) consists of patients with younger age at onset of Crohn's disease and long duration of disease before cancer development. The second group (4 of the 30 patients in our series) consists of patients who present with late-onset Crohn's disease (patients older than 55 years) and short duration of disease⁴¹ or simultaneous Crohn's disease and cancer diagnosis.²⁹ Because onset of Crohn's disease in the sixth decade of life is relatively unusual and the incidence of spontaneous colorectal cancer is higher in the late decades, patients in this latter group could represent either spontaneous cancers or colitis-associated cancers arising in a setting of long-standing undiagnosed Crohn's disease.

Thompson et al.⁴² recognized the occult nature of intestinal cancer in Crohn's disease. They found that 59%

of all cancers and 33% of colorectal carcinomas complicating Crohn's disease were discovered only at operation. Similarly, 14 (47%) of our patients did not have their cancer diagnosed before surgery. Because tumor symptoms mimic those of the underlying disease, the recognition of a cancer arising in inflamed bowel becomes difficult. Therefore, delayed diagnosis appears to be the major reason for these tumors often being diagnosed in late stages, although some reviews describe more diagnoses in early stages.⁴³

The prognosis of ulcerative colitis-associated colorectal cancer initially was believed to be poor.⁴⁴⁻⁴⁶ Subsequent studies have shown that the prognosis differs little from that of spontaneous colorectal cancer.⁴⁷⁻⁴⁹ The current study showed that survival with Crohn's disease-associated colorectal cancer is similar to that of spontaneous colorectal cancer, and it supports the findings of Choi and Zelig,⁵⁰ who reported an almost identical 5-year survival among patients with ulcerative colitis and Crohn's disease-associated colorectal cancers (50% vs. 46% at 5 years). The 44% 5-year survival rate (56% for in-continuity cancer) observed in our series is at least as good as that reported for spontaneous large-bowel cancer (30-47%)^{33,34} and for ulcerative colitis-associated colorectal cancer (36-55%).^{34,35} Although we censored four patients whose deaths were not related to colorectal cancer, our survival rate represents a minimum figure, because it includes 2 patients who died after surgery and 14 patients who did not have curative resections. Patients with Crohn's disease-associated colorectal carcinoma have a considerable mortality rate in the first 2 to 3 years after surgery; all 15 cancer-related deaths in the current study occurred within 29 months, including one patient with early-stage cancer (stage B). However, long-term survival can be expected thereafter, a feature that we had observed in patients with ulcerative colitis-associated colorectal carcinoma.⁴⁷

Patients with tumor in excluded bowel have an ominous prognosis because they generally present with advanced cancers. In our series, four of five such patients had advanced-stage cancer, and all five died of colorectal cancer. However, because bowel exclusion as a surgical treatment of Crohn's disease is no longer popular, the number of cancers arising in the excluded large bowel can be expected to drop. Therefore, the 56% 5-year survival rate for patients with Crohn's disease with in-continuity cancer becomes extremely meaningful, because we can expect a greater proportion of these patients to constitute the population with cancer in the coming years.

In conclusion, colorectal carcinoma complicating Crohn's disease appears to be similar to that in ulcerative colitis in many respects. Long duration of disease is the principal risk factor for cancer development in both types of inflammatory bowel disease. The 5-year survival

rate of 56% in the current study for patients without excluded loops is similar to that reported for ulcerative colitis-associated large-bowel cancer. Most patients present with advanced lesions, possibly because the cancer symptoms may overlap those of the underlying disease. These observations again raise the question of the advisability of a surveillance program for patients with longstanding Crohn's disease, especially when it involves the colon, similar to the current practice for ulcerative colitis.^{14,51,52}

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