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COLORECTAL CARCINOMA IN PATIENTS LESS THAN 40 YEARS OF AGE: PATHOLOGY AND PROGNOSIS

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ABSTRACT: Clinicopathologic features in 35 patients below the age of 40 years with colorectal carcinoma were reviewed and compared with those of a control group containing 409 patients ranging from 40 to 74 years of age. All cases in this series were experienced at the First Department of Surgery, Nagasaki University School of Medicine, during the 18 years from 1970 to 1988. 1) Young patients accounted for 6.7% of all cases with colorectal cancer, and this group included more female patients than in the elderly control group. 2) The young patient group presented with advanced lesions (Dukes' stage C) in 54.3% of cases compared with 35.6% of the old patient group with significantly high incidences of lymph node involvement. There were no significant differences in the hepatic metastasis and peritoneal dissemination among two groups. 3) Mucinous carcinoma and vascular invasion were frequently found on histologic examination in the young group, which suggested the highly malignant potentiality, but no significant difference in DNA ploidy pattern was observed between the young and the control group. 4) Curative resection rates were 71.4% in young and 68.1% in elderly patients. Overall 5-year survival was 56.9%. Five-year survival in 25 patients undergoing potentially curative resection increased to 74.4% with the similar rates of the control group. Improved 5-year survival following potentially curative resection stresses the need for early diagnosis and treatment.

INTRODUCTION

Recently in Japan, colorectal carcinoma increased in frequency with increasing age. The disease has its peak incidence in the fifth and sixth decades of life, and is uncommon in patients of age less than 40 years. Several reports have established that the prognosis of colorectal carcinoma for patients younger than

40 years of age is poorer than that of the general population¹⁻⁴⁾. This is probably due to delayed diagnosis because colorectal carcinoma seldom affects young adults. In addition, the biological behavior of the tumor is more aggressive than in the adults older than 40 years of age, with a higher incidence of undifferentiated and mucinous tumors and a higher incidence of Dukes C and D patients^{3, 4, 10)}. However, the recent study suggests that the prognosis for

patients in this age group may be similar to that reported on the older patient population^{5-9, 11-14}. The present study was undertaken to reevaluate the pathology and prognosis of colorectal cancer in young adults of age below 40 years.

PATIENTS AND METHODS

Five hundred and nine patients with colorectal cancer were surgically treated at The First Department of Surgery, Nagasaki University School of Medicine, during a period of 18 years between 1970 and 1988. Of these 509, 35 (6.9%) were less than 40 years of age (young group) and 409 (80.4%) ranged from 40 to 75 years of age (control group) at the time of diagnosis and/or operation. The two groups were compared with respect to age, sex, distribution of tumors, hepatic metastasis, peritoneal dissemination, histologic classification, lymphnode metastasis, Dukes' classification, rate of curative resection, and prognosis. Those cases associated with ulcerative colitis or familial polyposis were excluded. Cellular DNA content was also measured in paraffin-embedded materials from 235 cases of colorectal cancer available by flow cytometry (FCM) according to the Schutte's method¹⁶. Pathological findings were evaluated on the basis of the General Rules for Clinical and Pathological Studies on Cancer of Colon, Rectum and Anus¹⁷. Survival was calculated using the Kaplan-Meier method.

RESULTS

Age and sex: The age distribution of all cases is detailed in **Table 1**. Four patients (0.8%) were 20 to 29 years of age, and 31 (13.4%) were 30 to 39 years of age. There was also a large number of patients in their 50s and 60s. The male to female ratio was 1.0:1.2 in the young group and 1.3:1.0 in the control group.

Location: The primary site of the tumor was shown in **Table 2**. There was a higher incidence of rectal tumors in the two age groups (42.9% in young and 42.8% in control group). However, the distribution differed slightly between the two age groups; the proportion of sigmoid tumors was lower in the age below 40 years compared with the older patients (8.6% and 29.3%

respectively). In the colon, left-sided tumors were more common in patients above the age of 40 years ($p < 0.05$), whereas tumors of the right colon including transverse colon were common in young patients.

Pathologic features

Gross appearance: Gross appearance of tumor according to Borrmann's classification was shown in **Table 3**. The type of Borrmann 2 was the most common in two groups and was found

Table 1. Age and Sex Distribution

Age	No. of Patients	Men	Women
20-29	4	2	2
30-39	31	14	17
40-49	68	43	25
50-59	117	64	53
60-69	169	87	82
70-79	97	55	42
80-89	22	14	8
90	1		1
Total	509	279	230

Table 2. Site Distribution of Colorectal Carcinomas

Site	<40 yrs		40-75 yrs	
	No.	%	No.	%
Caecum	3	8.6	28	6.8
Ascending colon	3	8.6	30	7.3
Transverse colon	6	17.1	19	4.6
Descending colon	3	8.6	18	4.4
Sigmoid colon	3	8.6	120	29.3*
Rectum	15	42.9	175	42.8
Anus	2	5.7	19	4.6
Total	35	100	409	100

* $p < 0.05$

Table 3. Macroscopic Findings of Colorectal Carcinomas

Macroscopic Findings	<40 yrs		40-75 yrs	
	No.	%	No.	%
Early cancer	2	5.7	11	2.7
Advanced cancer				
Borrmann 1	4	11.4	41	10.0
Borrmann 2	19	54.3	289	70.7*
Borrmann 3	9	25.7	63	15.5
Unclassified			5	1.2
Total	35	100	409	100

* $p < 0.05$

in more than half of the total number of cases (53.4 percent in the young group versus 70.5 percent in the control group). However, the type of Borrmann 3 was more often encountered in the young group (25.7%) than in the control group (15.5%, $p < 0.05$).

Cell differentiation: In the young group, 47.1% were well differentiated, 41.2% moderately and 4% mucinous carcinoma, and none was poorly and undifferentiated. A slightly higher proportion of mucinous carcinoma was observed in the young group than the control group (**Table 4**). *Microscopic vascular and lymphatic invasion (v- and ly-factor)*: Higher invasion of microscopic vessels was noted in the young group than in the control group ($p < 0.05$) (**Table 5**). However, there was no significant difference in the microscopic lymphatic invasion.

DNA analysis: Of 12 young patients studied, 5 (41.7%) had aneuploid lesions and 7 (58.3%) had diploid tumors, whereas 134 out of 235 patients (59.8%) in the control group had aneuploid tumors and 90 had diploid tumors. There was no significant difference in the incidence of

aneuploid tumors among two groups.

Lymph node involvement: The incidence of lymph node involvement was higher in the young group (65.7%) than in the control group (49%, $p < 0.05$). Of the patients with lymph node involvement, 77.2% in the young group and 55.4% in the control group presented with metastasis in the intermediate or more distant lymph nodes (**Table 6**). Thus, there was a higher degree of lymph node involvement in the young group ($p < 0.05$).

Hepatic metastasis and peritoneal dissemination: Hepatic metastasis reviewed on the basis of macroscopic findings at operation was found in 5.7% of the young patients and 10.8% of the elderly patients (not statistically significant). And no significant difference of peritoneal dissemination was noted among two groups (8.6% in the young and 5.2% in the control) (**Table 7**).

Dukes' staging: In the young group, Dukes' C lesions were most frequent (54.3%), followed by Dukes' B lesions (20%), Dukes' D lesions (14.3%) and Dukes' A lesions (11.4%). In the control

Table 4. Histological Findings of Colorectal Carcinomas

Histology	<40 yrs		40-75 yrs	
	No.	%	No.	%
Adenocarcinoma				
Well	16	47.1	166	40.5
Moderately	15	41.2	200	48.9
Poorly			19	4.6
Mucinous Carcinoma	4	11.8	17	4.2
Undifferentiated			4	1.0
Others			2	0.5
Total	35	100	409	100

Table 5. Microscopic Invasion of Venous and Lymphatic Vessels in Colorectal Carcinomas

Microscopic Invasion	<40 yrs		40-75 yrs	
	No.	%	No.	%
Venous				
v (-)	9	25.7	184	45.0
v (+)	26	74.3	225	55.0*
Lymphatic				
ly (-)	6	17.1	91	22.2
ly (+)	29	82.9	318	77.8

* $p < 0.05$

Table 6. Lymph Node Involvement of Colorectal Carcinomas

Grade of lymph node Involvement	<40 yrs		40-75 yrs	
	No.	%	No.	%
n ₀	12	34.3	208	50.9
n ₁	6	17.1	89	21.8
n ₂	13	37.1	77	18.8
n ₃	3	8.6	24	5.9
n ₄	1	2.9	11	0.2
Total	35	100	409	100

Table 7. Tumor Stage According to Duke's Classification and Metastasis

Duke's stage	<40 yrs		40-75 yrs	
	No.	%	No.	%
A	7	20.0	118	28.9
B	4	11.4	79	19.3
C	19	54.3	145	35.5*
D	5	14.3	67	16.4
Total	35		409	
Metastasis				
Hepatic	5	5.7	49	10.8
Peritoneal	3	8.6	21	5.2

* $p < 0.05$

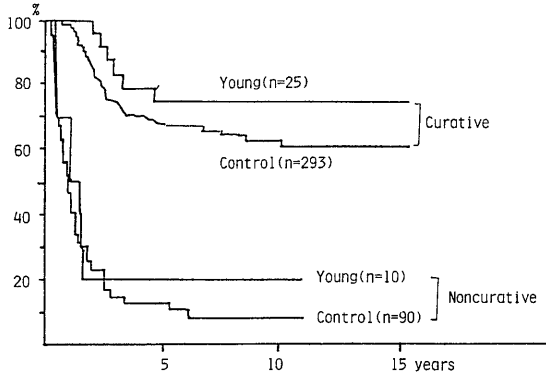


Fig. 1. Survival rates of patients with colorectal carcinoma
 Young: Patients below 40 years of age
 Control: Patients ranging from 40 to 74 years of age

group, Dukes' C lesions were also found in the largest proportion of patients (35.6%), followed by Dukes' B lesions (29%), Dukes' A lesions (18.7%) and Dukes' D lesions (16.5%). The difference in the incidence of Dukes' C lesions between the two groups was significant ($p < 0.05$) (Table 7).

Operation and Survival

The rate for curative resection in the young group (71.4%) was slightly lower than that in the control group (76.0%), but the difference was not statistically significant.

The prognosis of colorectal carcinoma was evaluated on the basis of the Kaplan-Meier method in the total groups of patients with resection and in those with curative resection. The overall 5 year survival rate was not significantly different among the two groups (56.9% versus 54.7%), and the survival rate for curative resection in the young group (74.4%) also showed no significant difference from that in the control group (68.1%) (Fig. 1).

DISCUSSION

Colorectal carcinoma, which frequently occurs among relatively old patients with a peak incidence in the fifth and sixth decade of life, is uncommon in patients younger than 40 years of age. The present series showed that the incidence peaks in patients in their 50s and 60s

Table 8. Incidence of Patients below 40 Year of Age with Colorectal Carcinoma (Japan, United States, Europe)

Author	Year	No. of patients	%	Male/Female
Okuno <i>et al</i> ¹¹⁾	1987	57	10.0	1 : 1.18
Kanda <i>et al</i> ¹²⁾	1988	51	4.8	26 : 25
Ohhigashi <i>et al</i> ¹³⁾	1989	17	4.3	1 : 1.13
Urakawa <i>et al</i> ¹⁴⁾	1990	9	3.3	1.3 : 1
Ohman <i>et al</i> ⁷⁾	1982	48	4.5	23 : 25
Umpleby <i>et al</i> ⁶⁾	1987	85	2.5	45 : 40
Domerque <i>et al</i> ⁴⁾	1988	93	3.6	40 : 38
McGillivray <i>et al</i> ⁹⁾	1991	50	6.2	33 : 17
Present study	1991	35	6.7	1 : 1.19

at the time of operation. However, patients younger than 40 years of age accounted for 6.7 percent of the cases (35 out of 509 cases); therefore, colorectal cancer in this age group is not so rare. Although some investigators have proposed defining the age range for young patients with colorectal cancer as being less than 35 years or 30 years of age^{15, 18)}, the majority of literatures in large series have referred to the age less than 40 years as the appropriate age range for young patients. These papers were reported on the basis of the data of Bedikian *et al*³⁾, who studied the clinicopathologic pattern of colorectal carcinoma, and detected no differences between patients in their 20s and 30s.

The incidences of young patients younger than 40 years of age which were reported from Japan, United States and Europe were listed in Table 8. It was found that the incidence varied from 3.3 to 10.0% in Japanese series and 2.5-6.3% in most series of the United States and Europe.

Sixteen of our 35 young patients with colorectal carcinoma were male and 19 were female. The incidence of young female patients was significantly higher than that in the control group. However, the majority of the recent series in the United States and Europe have reported higher incidences in male patients.

A progressive increase in the incidence of sigmoid lesions has been noted for the general population in Japan¹⁹⁾. However, some series reported a higher proportion of lesions to be right-sided in young patients^{3, 11)}. In the present series a higher incidence of transverse tumors and a lower incidence of rectosigmoid tumors were also found in young patients compared to

the patients older than 40 years of age.

As for the 'stage' of neoplastic lesions in young patients, it has been pointed out by many authors that it is already advanced at the time of diagnosis or at surgery. Kanai *et al* evaluated the clinicopathologic factors for aggressive disease in patients below 40 years of age with rectal cancer, and demonstrated four significant parameters, that is, depth of mural invasion, lymph node involvement, peritoneal dissemination, and rate of curative resection²⁰. While we compared retrospectively the histopathological findings of tumor, the incidence of distant metastases and peritoneal dissemination, the rate of curative resection, macroscopic findings of tumors, lymph node involvement, depth of mural invasion and microscopic invasion of cancer cells into the venous and lymphatic vessels were analyzed in patients who underwent tumor resection. We agree with Kanai's report that the significant differences for lymphatic involvement and Dukes C between young and control patients were recognized. A slightly higher rate of Borrmann 3 and positive venous invasion were also observed in the young group. Those parameter could be associated with advanced disease, but this series showed no significant differences for hepatic metastasis and peritoneal dissemination among two groups.

Many authors postulate that a more biologically aggressive tumor occurs in young patients, based on the finding of a higher percentage of poorly differentiated and mucin-producing cancer^{3, 14}. In this series, the percentage of mucin-producing tumors (12 percent) in young patients was slightly higher than that in the control group, but none was poorly differentiated.

Recently, many reports have suggested that the DNA content of the tumor was important for the prognosis, but a few have been studied on colorectal tumors of young patients. Heimann and his co-workers at the Mount Sinai Hospital in New York analyzed 50 cases of colorectal carcinoma in patients under 40 years of age²¹. They found that 52 per cent were diploid and 21 per cent were aneuploid, in which this incidence was similar to that in the general population, and concluded that patients

developing colorectal cancer when they were younger than 40 years did not appear to have more aggressive tumors as determined by the incidence of DNA content abnormalities and histologic grading of the lesions. Our data is similar to those of Heimann's study. The aneuploid tumor may lead to rapid dissemination of the disease and worse prognosis of patients as has been noted for some other human tumors. But the results of this report must be confirmed by additional data based on a large group of patients.

There are considerable differences in reported rates of curative resection for young patients with colorectal cancers. A lower rate of curative resection among young patients than among other age groups have been reported¹¹⁻¹³, whereas some studies have not detected any difference^{4, 7, 14, 18}. The rate of curative resection in our young patients was slightly lower than that in the control patients. These results seem to reflect the fact that the stage of the lesion was advanced in a large proportion of our young patients.

The prognosis of colorectal cancer in young patients had been considered unfavorable in the earlier reports. Five-year survival was quoted from as low as 8% to 21%^{1, 2}. This was attributed to delayed diagnosis and the aggressive biological behavior of the tumor, such as poorly differentiated carcinoma and mucinous carcinoma in this age group. However, most of the recent series reported no difference in the overall 5-year survival and in the survival rate

Table 9. Five-year Survival Rates of Young Patients with Curative Resection Compared to Old patients

Author	5-year survival of young patients	Comparison for old patients
Okuno <i>et al</i>	71.6	Same
Kanda <i>et al</i>	86.7	Better
Ohhigashi <i>et al</i>	100	Same
Urakawa <i>et al</i>	66.7	Same
Martin <i>et al</i>	70.8	Same
Ohman	50	Same
Beckman <i>et al</i>	59	Better
Umpleby <i>et al</i>	59	Same
Domerque <i>et al</i>	30	Worse
McGillivray <i>et al</i>	43	Same
Present study	74.4	Same

after curative resection between those below 40 years and those above 40 years of age (**Table 9**). In the present series, there were no significant differences in survival rate between the young and control groups. Our results also coincide with recent studies of young colorectal cancer patients which showed overall 5 year survival rates of 17.9-56.0% and 'curative' 5 year survival rates of 30-100%, and revealed marked increases in comparison to those in earlier studies. This was attributed to improved diagnosis, better surgical techniques, and was evidenced by the 74.4 percent five-year survival in those having potentially curative resection and the overall five-year survival of 56.9 percent.

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