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Long-Term Outcome and Prognostic Factors of Sporadic Colorectal Cancer in Young Patients

A Large Institutional-Based Retrospective Study

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Abstract: The prognosis of early-onset sporadic colorectal cancer (CRC) patients remains controversial. The objective of this study was to assess the long-term outcome and prognostic factors of sporadic CRC in young patients.

From 2006 to 2011, 8207 patients underwent curative or palliative surgery for CRCs in our institution. A total of 693 patients who were ≤45 years old with sporadic CRC were enrolled as the young group. A total of 1823 patients aged between 56 and 65 years were identified as middle-aged control group for this study. Survival outcome and prognostic factors were compared between the two groups.

Young patients had higher recurrence rate than older patients in stages I and II (8.8% vs 2.7%, $P < 0.001$). There was no significant difference of recurrence rate in stage III and IV cancers (27.5% vs 27.9%, $P = 0.325$). Metachronous cancers were developed more frequently in young patients (1.4% vs 0.6%, $P = 0.038$). Advanced stage CRC was diagnosed significantly more common in the young group (55.6% vs 47.9%, $P = 0.001$). High microsatellite instability (MSI) tumors are less likely to have advanced stage cancers (odds ratio (OR) 0.23, 95% confidence interval (CI) = 0.07–0.70) or cancer recurrence (OR 0.11, 95% CI = 0.01–0.85) in young patients. Cancer-specific survival was worse in young patients than that in older patients (81.2% vs 87.8%, $P < 0.001$). However, there was no significant difference in cancer-specific survival for each stage between the two groups. Independent prognostic factors for survival in young patients were undifferentiated cancer (hazard ratio (HR) 2.30, 95% CI = 1.23–4.31) and 3 months or longer duration of symptom (HR 2.57, 95% CI = 1.34–4.94). Young women had better survival compared with young men (HR 0.55, 95% CI = 0.33–0.90).

Prognosis of sporadic CRC in young patients is poorer than older patients, because of poorer histologic differentiation and delay in diagnosis. Early detection of CRC confers survival benefit to young patients. Because of higher recurrence rate and metachronous cancer risk, post-operative surveillance is also important in young patients.

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Abbreviations: AJCC = American Joint Committee on Cancer, CI = confidence interval, CRC = colorectal cancer, HR = hazard ratio, IHC = immunohistochemistry, MMR = mismatch repair, MSI = microsatellite instability, OR = odds ratio.

INTRODUCTION

Colorectal cancer (CRC) is the fourth frequently diagnosed malignancy overall and the second leading cause of cancer-related death in the world. The 2010 Annual Report to the Nation on the Status of Cancer documented continued declines of the incidence and mortality rates of CRC.¹ Such decline has been greatly affected by CRC screening colonoscopy and the removal of colorectal precancerous lesion, recommended for aged ≥50 years.² The majority of CRCs are developed in patients at 50 to 70 years of age. However, the age of CRC diagnosis in patients is getting younger and the incidence of CRC is increasing in people <50 years.

A number of reports^{3–7} about the clinical features and outcomes of young patients with CRC have been published over the last few decades. Nearly all reviews have reported that CRC in young patients have specific clinicopathologic features, including poorer histologic types and advanced-stage cancers at diagnosis. Young patients with CRC have not attained the same improvements in overall survival as older patients. One possible reason might be that the young patients with CRCs exhibit unique biologic characteristics, resulting in differences in clinical and treatment resistance behaviors.^{8,9} Therefore, a better understanding of young CRCs guides us to identify diagnostic and treatment approaches for young patients. The association between age and overall survival is inconsistent from previous studies. Most important limitation of previous reports was their heterogeneous study population including sporadic and hereditary CRCs. Hereditary CRCs such as Lynch syndrome commonly encountered in young patients and CRCs with Lynch syndrome have better prognosis and different biologic characteristics compared with sporadic CRCs. In the present study, we could exclude Lynch syndrome patients diagnosed with CRC strictly by routinely performing immunohistochemistry (IHC) for mismatch repair (MMR) proteins and microsatellite instability (MSI) analysis in tumor tissues.^{10,11}

The objective of this study was to evaluate the survival outcome and poor prognostic factors of sporadic CRC in

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young patients. We also defined distinct clinicopathologic characteristics of sporadic CRC in young patients from that in older patients. Furthermore, we identified risk factors for advanced-stage disease and survival to suggesting a potential role for screening and prompt evaluation for young CRC patients.

METHODS

Patients

This was a retrospective review of patients who underwent curative or palliative resection for CRC at Samsung Medical Center between 2006 and 2011. Figure 1 shows the histogram for a total of 8207 patients who underwent their first operation for CRC. These patients were classified into two groups according to their age. To identify specific clinicopathologic features and outcomes of young onset CRC, we defined “young” age patients as those within the bottom 10th percentile (≤ 45 years old) in the age histogram and compared them with patients representative of the typical age of sporadic CRC. We classified the control group as middle-aged patients within a 10 year range around the median age (61 years old) in the histogram. The majority of CRC were included in the median-aged 10 year range at our institution. Accordingly, 788 patients <45 years were classified into the young age group and 1823 patients of 56 to 65 years age were classified into the middle-aged group.

Among the 788 young patients with CRC, 19 patients with FAP, hamartomatous polyposis, or discrepancies between IHC and MSI analyses were excluded. In the remaining 769 patients, MSI analysis and IHC staining for MLH1, MSH2, and MSH6 were performed in 738 (95.9% of total) patients (supplementary material, <http://links.lww.com/MD/A958>). Of 94 patients who showed MSI-high CRCs with MMR protein loss, 34 refused to go for the germline mutation test. A pathogenic mutation in one of the MMR genes was found in 42 patients with Lynch syndrome. The remaining 18 patients lacked a germline mutation in MMR genes. Therefore, we excluded 42 patients with Lynch syndrome and 34 patients whose possibility of Lynch syndrome could not be ruled out. Finally, we enrolled 693 patients with nonhereditary CRC into the study population. This study was approved by the Institutional Review Board of the Samsung Medical Center (IRB number 2015-09-133).

Data Collection

The demographics, clinicopathologic characteristics, and data pertaining to operation and follow up of patients were

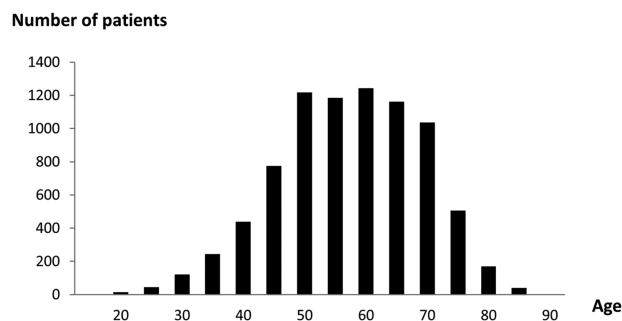


FIGURE 1. Age histogram for all of the patients (number = 8207) with colorectal cancer who underwent surgeries at our hospital. Tenth percentile age value was <45 years. The median age was 61 years.

reviewed. Data on demographics and clinicopathologic features included age, sex, family history of CRC, presenting symptoms leading to diagnosis, interval between symptom onset and diagnosis, tumor location, histologic type, MSI status of tumor, depth of invasion, lymph node metastases, distant metastases, and TNM stage based on the American Joint Committee on Cancer (AJCC) 7th edition.¹² Data of operation and follow up included the type of surgery, recurrence, survival time, and cancer-specific survival.

Statistical Analysis

Continuous variables were reported as mean \pm standard deviation, whereas categorical variables were presented as frequencies and percentages. Differences between continuous variables were compared using the Student *t* test, whereas differences between categorical variables were analyzed using the chi-squared test. Mortality data were obtained from the medical records or database of national health insurance and included the date and cause of death. Logistic regression analysis was performed to evaluate the potential association between clinicopathologic characteristics and survival. A *P*-value <0.05 was considered as statistically significant. Statistical analyses were performed using SPSS version 18 (SPSS Inc., Chicago, IL).

RESULTS

Baseline Characteristics

The baseline characteristics of the two CRC groups are summarized in Table 1. The median age of the young CRC group was 38 (range, 22–45) years. This group comprised 46.9% of female patients, which was higher than the proportion of female patients in the middle-aged CRC group at 36.5%. A total of 78 patients in the young group had a family history of CRC. The number of patients with family history in the young group was significantly more than that in the middle-aged group (11.5% vs 8.3%, $P = 0.021$). The majority of tumors (82.5%) were located distal to the splenic flexure. About half of tumors were located in the rectum in the young group, which was significantly higher than that in the middle-aged group (48.6% vs 40.8%, $P = 0.002$). Accordingly, low anterior resection or anterior resection was most commonly (87.0%) performed in the young group.

Histologically, undifferentiated cancers in the young group were significantly more frequent than that in the middle-aged group (9.4% vs 4.9%, $P < 0.001$). The proportion of patients who had 4 or more lymph node metastases (N2) was higher in the young group than that in the middle-aged group (26.4% vs 19.3%, $P < 0.001$). Advanced stage CRC was diagnosed significantly more in the young group (55.6% vs 47.9%, $P = 0.001$) (Figure 2). No significant difference in MSI status was observed between the young group and the middle-aged group. Metachronous cancers were developed more frequently in the young group compared with that in the middle-aged group (1.4% vs 0.6%, $P = 0.038$). However, there was no significant difference in the prevalence of synchronous cancers between the two groups.

TABLE 1. Clinicopathologic Characteristics of Colorectal Cancer in Young Patients and Middle-Aged Patients

	Young Patients (n = 693, %)	Median-Aged Patients (n = 1823, %)	P Value
Mean age (range)	38 (22–45)	60 (56–65)	
Sex			<0.001
Male	368 (53.1)	1158 (63.5)	
Female	325 (46.9)	665 (36.5)	
Family history	78 (11.5)	151 (8.3)	0.021
Tumor location			0.002
Rectum	337 (48.6)	738 (40.8)	
Left side colon	235 (33.9)	683 (37.5)	
Right side colon	119 (17.3)	386 (21.2)	
Type of surgery			0.042
LAR or AR	497 (71.7)	1253 (68.7)	
Right hemicolectomy	106 (15.3)	356 (19.5)	
Left hemicolectomy	26 (3.8)	94 (5.2)	
Total/subtotal colectomy	8 (1.2)	16 (0.9)	
Transverse colectomy	10 (1.4)	15 (0.8)	
Proctosigmoidectomy	10 (1.4)	13 (0.7)	
Abdominoperineal resection	16 (2.3)	39 (2.1)	
Endoscopic resection or TEM	20 (2.9)	37 (2.0)	
pT stage			<0.001
1	97 (14.0)	221 (12.1)	
2	94 (13.6)	303 (16.6)	
3	366 (52.8)	1048 (57.5)	
4	136 (19.6)	250 (13.7)	
pN stage			<0.001
0	320 (46.2)	964 (52.9)	
1	190 (27.4)	508 (27.9)	
2	183 (26.4)	351 (19.3)	
M stage			<0.001
0	606 (87.4)	1725 (94.6)	
1	87 (12.6)	98 (5.4)	
AJCC stage			<0.001
I	144 (20.8)	418 (22.9)	
II	164 (23.7)	531 (29.1)	
III	298 (43.0)	776 (42.6)	
IV	87 (12.6)	98 (5.4)	
Advanced stage (III or IV)	385 (55.6)	874 (47.9)	0.001
Histological type			<0.001
Well/moderate	592 (85.4)	1672 (91.7)	
Undifferentiated	65 (9.4)	90 (4.9)	
Poorly	52 (7.5)	75 (4.1)	
Signet ring cell	13 (1.9)	15 (0.8)	
Mucinous	36 (5.2)	60 (3.3)	
MSI status			0.156
Stable	607 (94.8)	1668 (92.9)	
Low	5 (0.8)	29 (1.6)	
High	28 (4.4)	99 (5.5)	
Synchronous cancer	10 (1.4)	47 (2.6)	0.088
Metachronous cancer	10 (1.4)	11 (0.6)	0.038

AJCC = American Joint Committee on Cancer, AR = anterior resection, LAR = low anterior resection, MSI = microsatellite instability, TEM = transanal endoscopic microsurgery.

Presenting Symptoms and Symptom Duration

Presenting symptoms and symptom duration before diagnosis are summarized in supplemental Table 1, <http://links.lww.com/MD/A958>. Most patients (80.5%) of the young group had symptoms before CRC diagnosis. The most commonly presented symptom was hematochezia. The portion of

asymptomatic patients who were diagnosed through screening program in the young group was lower than in the middle-aged group (19.5% vs 33.1%, $P < 0.001$). Intervals between symptom onset and diagnosis in the young group (average 52.9 days) were longer than in the middle-aged group (33.2 days). The portion of patients with delayed diagnosis (≥ 3 months duration

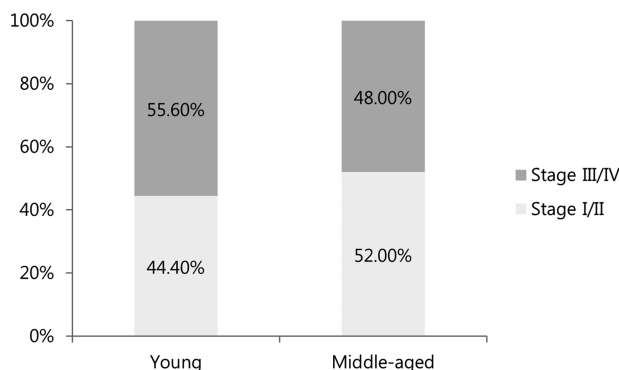


FIGURE 2. Stage distribution in young-age patients or middle-aged patients.

of symptom) in the young group was higher than in the middle-aged group (14.9% vs 7.9%, $P < 0.001$).

Risk Factors for Advanced Stage Disease

Results of logistic regression analysis of risk factors for advanced stage disease are shown in Table 2. Undifferentiated histologic type was a significant predictive factor for advanced stage in the both groups (young group: odds ratio (OR) 2.77, 95% confidence interval (CI) 1.24–6.18; middle-aged group: OR 4.12, 95% CI 1.60–10.56). The presence of symptoms before CRC diagnosis was identified as significant predictive factor for advanced disease in the both group (young group: OR 1.85, 95% CI 1.14–3.02; middle-aged group: OR 2.26, 95% CI 1.68–3.04). In contrast, high MSI status of tumor was a significant preventive factor for advanced disease in the both group (young group: OR 0.23, 95% CI: 0.07–0.70; middle-aged group: OR 0.15, 95% CI 0.05–0.42). Longer duration of symptom before diagnosis increased the risk of advanced stage only in the young group. Duration of 1 to 3 months (OR 3.01, 95% CI 1.77–5.12) and ≥ 3 months (OR 6.33, 95% CI 3.05–13.12) increased the risk of advanced stage in the young group.

Recurrence Patterns and Risk Factors for Recurrence

Sites of recurrence are summarized in supplemental Table 2, <http://links.lww.com/MD/A958>. A total of 133 (23.1%) patients in the young group and 273 (13.8%) in the middle-aged group experienced recurrence after curative resection. There was no significant difference of recurrence rate in stage III and IV cancers. However, the recurrence rate of stages I and II in the young group was higher than that in the middle-aged group (8.8% vs 2.7%, $P < 0.001$). Metachronous cancers developed more frequently in young patients (1.4% vs 0.6%, $P = 0.038$).

Stepwise logistic regression analysis of risk factors for recurrence revealed that T, N stage, and tumor location (rectum) were significant predictive risk factors for recurrence in the middle-aged group (Table 3). In the young group, T and N stages were significant risk factors. High MSI status of tumor was the only significant preventive factor for recurrence in the young group (OR 0.11, 95% CI 0.01–0.85).

Survival Outcome and Prognostic Factors between the Young Group and the Middle-aged Group

The median follow-up duration for the young group and the middle-aged group was 66.4 (range 18–124) and 66.8 (range 14–114) months, respectively. The 5-year cancer-specific survival rate was 81.2% in the young group and 87.8% in the middle-aged group ($P < 0.001$). The 5-year survival rate for stage I in the young and middle-aged group was 98.5% and 98.1%, respectively ($P = 0.188$). The 5-year survival rate for stage II was 93.7% and 94.9% in the young and middle-aged group, respectively ($P = 0.771$). For stage III, it was 78.2% and 83.2% in the young and middle-aged group, respectively ($P = 0.087$). For stage IV, it was 39.0% and 49.9%, respectively ($P = 0.142$). Kaplan–Meier cancer-specific survival curves by each stage are shown in Figure 3. Cancer-specific survival of stages III and IV in the middle-aged group was relatively better than that in the young group. However, there was no significant difference in overall survival for each stage.

TABLE 2. Risk Factors for Advanced Stage of Colorectal Cancer

Factors	Young Patients (n = 693)		Middle-Aged Patients (n = 1823)	
	OR (95 % CI)	P Value	OR (95 % CI)	P Value
Differentiation				
Differentiated (well/moderate)	Reference		Reference	
Undifferentiated	2.77 (1.24–6.18)	0.013	4.12 (1.60–10.56)	0.003
Mucinous	2.21 (0.79–6.17)	0.131	2.15 (0.75–6.15)	0.153
Screening or Symptoms				
Screening	Reference		Reference	
Symptoms	1.85 (1.14–3.02)	0.013	2.26 (1.68–3.04)	<0.001
MSI status				
Stable	Reference		Reference	
High	0.23 (0.07–0.70)	0.01	0.15 (0.05–0.42)	<0.001
Symptom duration				
<1 mo	Reference		Reference	
1–3 mo	3.01 (1.77–5.12)	<0.001	1.28 (0.81–2.02)	0.3
>3 mo	6.33 (3.05–13.12)	<0.001	1.46 (0.81–2.62)	0.21

CI = confidence interval, MSI = microsatellite instability, OR = odds ratio.

TABLE 3. Risk Factors for Recurrence after Curative Resection

Factors	Young Patients (n = 693)		Middle-Aged Patients (n = 1823)	
	OR (95% CI)	P Value	OR (95% CI)	P Value
T stage				
T1	Reference		Reference	
T2	2.52 (0.76–8.32)	0.129	1.89 (0.38–9.48)	0.437
T3	3.02 (1.02–8.06)	0.046	4.61 (1.07–19.91)	0.041
T4	8.59 (2.67–27.69)	<0.001	10.21 (2.15–48.45)	0.003
N stage				
No	Reference		Reference	
N1	3.36 (1.95–5.78)	<0.001	1.78 (0.99–3.19)	0.053
N2	5.84 (3.25–10.49)	<0.001	3.68 (2.03–6.67)	<0.001
MSI status				
MSI stable	Reference		Reference	
MSI high	0.11 (0.01–0.85)	0.034	0.18 (0.02–1.39)	0.1
Histologic type				
Well/moderate differentiated	Reference		Reference	
Undifferentiated	0.60 (0.23–1.55)	0.29	1.29 (0.41–4.12)	0.67
Tumor location				
Colon	Reference		Reference	
Rectum	1.48 (0.94–2.33)	0.089	1.99 (1.22–3.24)	0.006

CI = confidence interval, MSI = microsatellite instability, OR = odds ratio.

The results of univariate and multivariate analyses of prognostic factors for cancer-specific survival in both groups are shown in Table 4. In the young group, multivariate analysis showed that undifferentiated histologic type (hazard ratio (HR) 2.30, 95% CI 1.23–4.31) and ≥3 months duration of symptoms (HR 2.57, 95% CI 1.34–4.94) were significant prognostic factors for cancer-specific survival. Significant prognostic factor for overall survival in the middle-aged group was advanced stage (III/IV) (HR 2.16, 95% CI 1.13–4.13) in multivariate analysis. Female sex was identified as the only good prognostic factor of survival in the young group (HR 0.55, 95% CI 0.33–0.90).

DISCUSSION

In this study, we provided relative large number of young sporadic CRC patients in a single center and excluded Lynch syndrome-associated hereditary CRC using molecular screening of MSI/MMR for the first time. Our results demonstrated that young CRC patients had distinct clinicopathologic characteristics and outcomes. Their sporadic CRC had more poorly differentiated carcinoma, mucinous carcinoma, and signet ring cell carcinomas. They presented with stage III or IV disease more frequently than older patients. The risk factors for young patient with advanced stage were undifferentiated histologic types and delayed diagnosis. Because of more advanced-stage diseases, cancer-specific survival was worse in young patients. However, there was no significant difference in cancer-specific survival for each stage of CRC between the two groups.

Our results demonstrated that young CRCs had more undifferentiated histologic cancers such as poorly differentiated carcinoma and signet ring cell carcinoma. In a recent SEER databases research also showed that young CRC patients had more aggressive pathology, such as poorer differentiation, and more mucinous/signet ring cell carcinoma.¹³ It has been reported that the molecular carcinogenesis for this specific type

of sporadic young CRC appears to involve a sub-type of the chromosomal instability pathway, with no involvement of the methylator pathway and no mutation of BRAF.¹⁴ In the present study, we excluded patients with hereditary CRC using MSI/MMR molecular screening. Despite this, young sporadic CRC patients had a higher rate of family history than older patients. However, relatively few molecular genetic studies of sporadic CRC have been conducted in young age group. Further studies are needed to confirm the role of such pathways in the carcinogenesis of sporadic young CRC.

In accordance with our results, previous studies have also shown that CRC in young patients tends to locate mostly on distal location. A cohort study based on large population using 64,068 young CRC patients has revealed that young-onset CRC more predominantly arise from the splenic flexure to rectum.¹⁵ Another large population-based cohort study analyzing 279,623 CRC patients from SEER data has also reported that 39.3% of CRCs in young patients (≤50 years) are located in the rectum. This proportion is decreased to 26.7% in patients >50 years of age.¹³ In this study, 48.6% of CRCs in young patients occurred in the rectum, which was much higher than that based on SEER database.¹³ The proportion of rectal cancer in Asia is higher than that in Western countries.¹⁶ This guides us to recommend sigmoidoscopy or digital rectal examination as cost-effective screening or diagnostic tools for young patients.

We found that the majority of young CRC patients were symptomatic. The most common symptoms were hematochezia, abdominal pain, and bowel habit change. This is similar to the literature review of 55 articles concerning young CRC patients. The two most common symptoms of CRC in that review are rectal bleeding and abdominal pain.⁶ Delayed diagnosis is a subject of interest because this factor contributes to the presentation of advanced stage cancers in young patients. However, the definition of “delay” is difficult to standardize. Two previous studies have commented on the duration of the delayed diagnosis. One study found that 26% of young patients

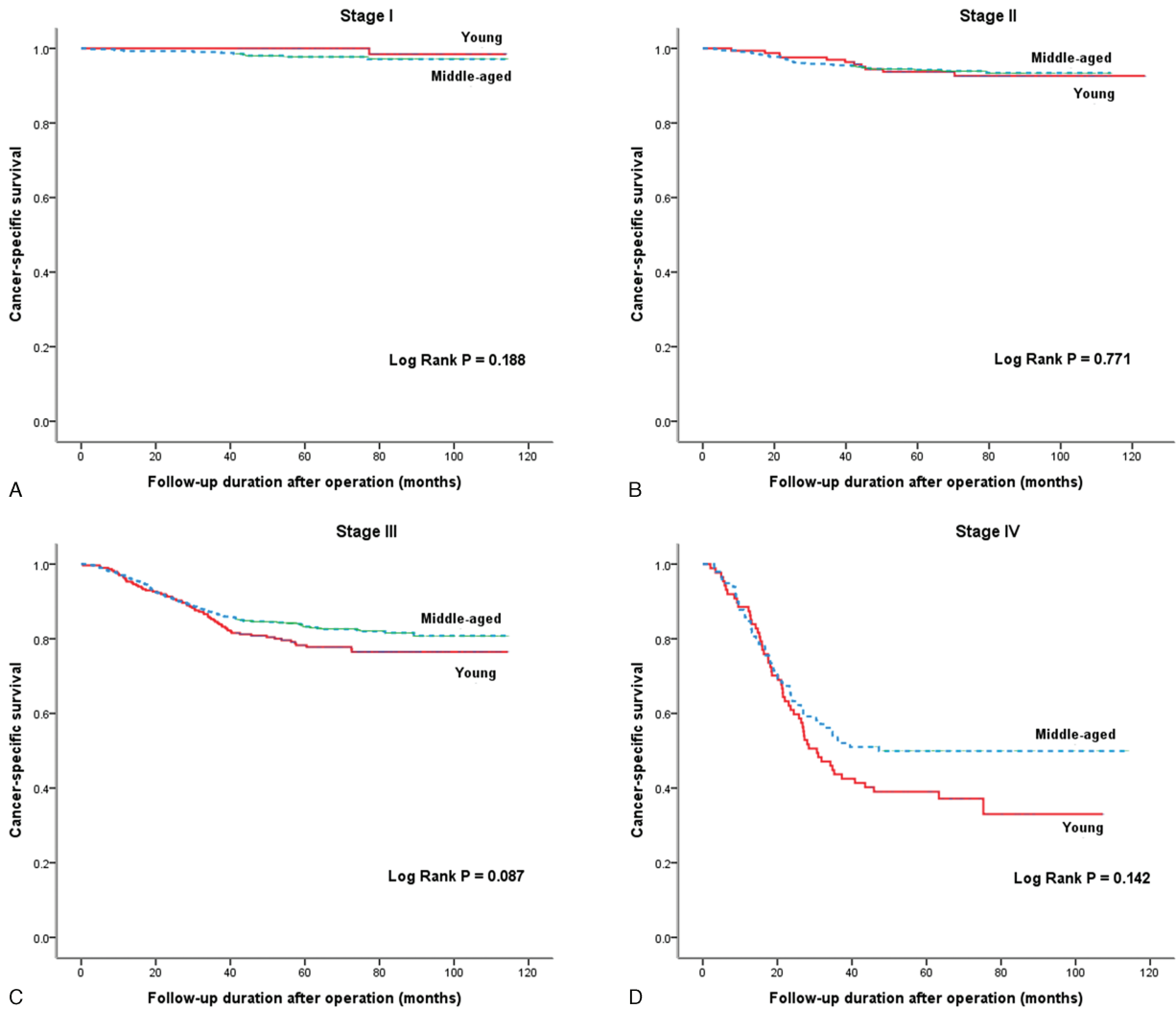


FIGURE 3. Kaplan–Meier survival curves for young patients and middle-aged patients by each stage of colorectal cancer: (A) stage I, (B) stage II, (C) stage III, and (D) stage IV.

had a 3-month delay in diagnosis, the other found that 45% of young patients had a delay of >6 months.^{17,18} In this study, we defined delayed diagnosis as a delay of >3 months. A total of 14.9% of young patients had a delay in diagnosis. Delayed diagnosis is multifactorial. It is associated with both patient-based factors and physician-based factors. These factors include: (1) absence of routine screening in young patients; (2) under-utilize healthcare services in young patients; (3) physician overlook or dismiss young patient’s symptoms that are nonspecific but may be consistent with CRC.

In the present study, young patients had more advanced stage cancers at stage III or IV compared with older patients. A systemic review has found an average of 66% of patients <40 years old were presented at stage III or stage IV.⁶ In addition, we found that undifferentiated carcinoma, symptomatic patient, and a delay in diagnosis were risk factors for advanced stage. Of these factors, delay in diagnosis was a risk factor for advanced cancers only in young patients. Overall, it appears that CRCs in young patients are more aggressive with pathologic and biologic characteristics compared with older patients. In contrast, high MSI status was strongly associated with a

lower stage of CRC in both groups. Gryfe et al have found that young CRC patients with high MSI tumors have improved survival. They are less likely to have metastatic disease to lymph nodes or distant organs compared with microsatellite stable tumors.¹⁹ Several studies have shown the high rates of MSI in young CRC patients.²⁰ In our study, we found no significant difference in MSI status between young and older patients and MSI was not a prognostic marker in both groups. A recent study reported that several molecular biomarkers such as PRL, RBMS, Wrap53, and DNA status are differentially expressed between young and older patients and they are prognostic biomarkers for young CRC patients.²¹

The prognosis of young CRC patients remains controversial.^{13,22,23} The largest cohort study analyzing 43,291 young CRC patients with long follow-up from databases in United States and Sweden has demonstrated that the 3, 5, and 10-year cancer-specific survival of young patients is significantly better than those of elderly patients with the same stage.²¹ However, we found that cancer-specific survival of stage III and IV was relatively better in older patients than in young patients. In our study, we excluded hereditary CRCs, particularly Lynch

TABLE 4. Results of Cox Proportional Hazards Analysis to Determine Prognostic Factors for Survival

Factors	Young Patients				Middle-Aged Patients			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95 % CI)	P Value	HR (95 % CI)	P Value	HR (95 % CI)	P Value	HR (95 % CI)	P Value
Sex								
Female	0.72 (0.51–1.01)	0.05	0.55 (0.33–0.90)	0.02	1.13 (0.86–1.49)	0.36		
Family history	1.39 (0.81–2.39)	0.23			0.88 (0.42–1.88)	0.75		
Tumor location								
Rectum	Reference				Reference			
Left side colon	1.05 (0.72–1.52)	0.81			1.01 (0.75–1.35)	0.95		
Right side colon	0.99 (0.63–1.56)	0.98			1.28 (0.90–1.83)	0.17		
MSI status								
Stable	Reference				Reference			
High	0.88 (0.12–6.31)	0.89			0.92 (0.41–2.08)	0.84		
Differentiation								
Differentiated (well/moderate)	Reference				Reference			
Undifferentiated	2.33 (1.51–3.58)	< 0.001	2.30 (1.23–4.31)	0.01	1.82 (1.28–2.60)	0.01		
Mucinous	1.00 (0.59–1.69)	0.99			1.10 (0.59–2.01)	0.78		
Advanced stage (III or IV)	2.24 (1.17–4.31)	0.02			2.10 (1.06–4.14)	0.03	2.16 (1.13–4.13)	0.02
Presence of symptoms	1.79 (0.83–3.88)	0.14			1.18 (0.67–2.08)	0.57		
Symptom duration								
<1 mo	Reference				Reference			
1–3 mo	1.41 (0.86–2.31)	0.17	1.62 (0.95–2.76)	0.08	1.05 (0.59–1.87)	0.87		
>3 mo	1.69 (0.99–2.91)	0.05	2.57 (1.34–4.94)	0.01	0.75 (0.41–1.35)	0.33		

CI = confidence interval, HR = hazard ratio, MSI = microsatellite instability, OR = odds ratio.

syndrome-associated CRCs, which have improved the survival outcome compared with nonhereditary CRC. This might explain the discrepancy between our results and the results of the largest cohort study. Independent prognostic factors for cancer-specific survival in young patients were undifferentiated carcinoma and a delay in diagnosis for >3 months. These factors were also risk factors for advanced stage associated with poorer survival. Young women had significantly better overall survival compared with young men. However, there was no gender difference for overall survival in older CRC patients. The protective effect of estrogen on CRC may be an important factor.²⁴

There were some limitations to this study. The major limitation was its retrospective design and this study was performed at a single tertiary referral center. Although small number of patients with MSI-high tumor refused to undergo the germline mutation test, there might be possibility of excluding MSI-high sporadic cancers. However, it should be noted that several studies have demonstrated that the majority of young patients with abnormal MSI and/or IHC have underlying germline mutations.^{25,26} This study also has several strengths. First, the study population was large and patients in this study were consecutively enrolled from a prospectively collected database. Second, the median duration of follow-up after surgery was 67 months. Third, we excluded hereditary CRC patients using MSI/MMR universal molecular screening because hereditary CRC have distinct screening, management strategy, and better survival outcomes compared with sporadic CRCs.^{27–29}

In conclusion, this study revealed that sporadic CRC in young patients had more aggressive histologic differentiation and poorer outcome than older patients. They had frequent synchronous metastatic disease with infrequent synchronous CRC. And they had more recurrent or metachronous cancers. Independent prognostic factors for young patients included undifferentiated carcinoma and delay in diagnosis. Early detection by screening for asymptomatic patients or by promptly evaluating symptomatic patients can confer survival benefit to young-onset CRCs. Considering the location of tumor and safety of patients, sigmoidoscopy might be good screening tool for young patients. Further studies are needed to identify novel diagnostic, prognostic, and predictive markers in this population. In addition, patients should be educated regarding the symptoms of CRC so that they can seek medical attention early.

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