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Young Patients (≤35years old) With Colorectal Cancer Have Worse Outcomes Due to More Advanced Disease

A 30-Year Retrospective Review

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Abstract: An appropriate cutoff of age and the impact of age on colorectal cancer outcomes remain unclear and need to be explored, particularly in China.

In total, 2460 colorectal cancer patients were studied retrospectively. All patients were divided into 6 groups according to their ages at the time of diagnosis: ≤30, 31 to 35, 36 to 40, 41 to 45, 46 to 50, and ≥50 years. A suitable cutoff age for defining young adult colorectal cancer was explored according to the distribution of survival in each group. Clinical characteristics and prognosis between the young adult group and the older group were then compared.

According to the survival curves for each group, 35 years old was considered a suitable cutoff age for defining young adult colorectal cancer. There were 140 (5.7%) and 2320 (94.3%) cases in the young adult and older groups, respectively. The proportion of stage III–IV tumors was significantly higher in the young adult group (69.3%) than in the older group (46.4%) ($P = 0.000$). The univariate analysis showed that the 5-year overall survival (OS) rate and the 10-year OS rate in the young adult group were 48.9% and 38.6%, respectively, whereas in the older group, they were 63.6% and 56.9%, respectively. The young adult group had a worse prognosis ($P = 0.000$). The multivariate analysis showed that age was not an independent prognostic factor (relative risk 0.787, $P = 0.062$). After adjusting for tumor stage, the hazard proportion of death in the young adult group increased by 27.6%, but this difference was not significant ($P = 0.053$). Stratified analyses showed that the young adults with stage IV tumors had a worse survival rate ($P = 0.046$).

Patients ≤35 years who were diagnosed with colorectal cancer had a worse prognosis because of a higher proportion of advanced stage tumors. When stage-to-stage analysis was performed, it was found that young adult colorectal cancer patients had a worse outcome only if they had stage IV tumors.

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Abbreviations: CI = confidence interval, OS = overall survival, RR = relative risk.

BACKGROUND

Colorectal cancer is the fourth most common cancer and the second leading cause of cancer-related deaths worldwide[1]; therefore, colorectal cancer poses a serious threat to public health. The majority of colorectal cancer patients are diagnosed between 50 and 70 years of age. However, the annual percentage of young patients being diagnosed with colorectal cancer is increasing,[2] and the median age at diagnosis is now younger.[2–4]

While the prognosis for thyroid cancer is favorable if the patient is diagnosed at a young age,[5] it is an unfavorable prognostic factor for breast cancer.[6] The impact of young age on the outcome of colorectal cancer remains controversial and varies widely in different regions.[2,7,8] Some studies have shown better outcomes in young patients compared with older patients, whereas other studies reported contradictory results.[2,9–17] Therefore, an appropriate cutoff age for the ''young'' subgroup needs to be established before examining the effect of age on cancer outcomes. The aim of this study is to determine the appropriate cutoff age and characteristics of colorectal cancer patients, particularly in a young subgroup, by retrospectively reviewing data from patients with colorectal cancer that were referred to a Chinese provincial oncology agency.

METHODS

In total, 2460 colorectal cancer patients who were admitted to the Second Affiliated Hospital of Zhejiang University School of Medicine and treated between December 1985 and December 2011 were included in this retrospective study. The criteria for inclusion were as follows: patients with pathologically confirmed colorectal cancer and patients who underwent operations, including palliative surgeries. Patients who presented with recurrent cancers, or congenital syndromes, such as Lynch syndrome and familial adenomatous polyposis, were excluded

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YY, SZ, and JF made substantial contributions to the conception and design of this study; JF, JY, YT, and MJ analyzed and interpreted the data; FW, YH, HC, and CY performed the research; YH and FW performed the follow-up and acquired the data; JF and JY wrote the manuscript; YY and JF decided to submit the manuscript for publication; JY submitted the manuscript for publication. All coauthors voluntarily contributed without funding from any institution. The research was supported by The National High Technology Research and Development Program of China (863 Program), No. 2012AA02A204.

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from the data analysis. The hospital's ethics committee approved this study. All of the patients provided written informed consent. The data obtained from the patients included their age, gender, tumor sites, histological type, surgical approach, tumor infiltration, number of metastatic lymph nodes, distant metastasis, and survival.

Tumors were staged according to the AJCC 7th edition TNM staging system.[18] All of the patients with stage 0 cancers were included in the stage I group for survival analysis. The tumor sites were described as the colon and rectum. Both the sigmorectal junction and the ileocecal junction were considered as the colon. Differentiation grading was classified as well, moderately, poorly, or unknown grade. Histological type was classified as tubular adenocarcinoma, papillary adenocarcinoma, mucinous cancer, signet ring cell cancer, undifferentiated cancer, or unclassified adenocarcinoma. The following 3 surgical approaches were used: R0 resection – a radical procedure that involves the complete removal of all tumors with a microscopic absence of tumor cells in surgical margins; R1 resection – a procedure that leaves microscopic tumor cells in surgical margins; and R2 resection – a palliative procedure in which either a bypass or ileostomy was conducted in patients with unresectable tumors.

Specific staff members in the oncology institution were responsible for collecting data from the patients and subsequently following up with the patients. Follow-up was conducted every 3 months for the initial 2 years, then every 6 months for 3 years, and finally once a year for the remaining period. The follow-up was completed by telephone or mail correspondence. The deadline for follow-up was July 2013. The follow-up lasted for 302 months (median 32.7 months). At the end of the study, 268 patients (10.9%) were lost to follow-up. The overall survival (OS) was calculated from the time of the patient's operation to their death caused by the colorectal cancer. However, there were 65 patients (2.5%) that died from other causes. Their data were censored when OS was calculated. Additionally, the patients lost to follow-up were also censored.

Data of all categorical variables were summarized using frequencies and percentages. The data were analyzed using the chi-square test. OS was calculated according to the Kaplan–Meier method. Survival rates were compared by the log-rank test. A multivariate analysis was performed using the Cox model. When the P value was <0.05, the difference was considered statistically significant. SPSS 16.0 (SPSS Chicago IL, USA) software was used for data analysis.

RESULTS

In total, 2460 colorectal cancer patients, ages between 18 and 97 years (median age 59 years old), were analyzed. As shown in Figure 1, the majority of patients were between the ages of 50 and 70 years old. In patients <50 years old, the incidence of colorectal cancer decreased with decreasing age (Figure 1). Based upon the age distribution diagram, either 30, 35, 40, or 45 years could be selected as a potential cutoff age. To determine the appropriate cutoff age, all patients were divided into 6 age groups ($\leq$30, 31–35, 36–40, 41–45, 46–50, and $>$50 years old). In Figure 2, the survival curves of the $\leq$30-, 31–35-, and 36–40-year-old groups were separated from each other, with worse prognosis in the younger groups, whereas the survival curves of the 36 to 40-, 41 to 45-, 46 to 50-, and $>$50-year-old groups merged together. Then, all of the patients were divided into either the young adult group or the older group using 30, 35, 40, 45, and 50 years old as the cutoffs (see Appendix, Supplemental Digital Content 1, Exploration of cutoff age, http://links.lww.com/MD/A73). Analyses stratified by stage (with stages I and II being pooled and stages III and IV being pooled) showed that the young adult group had a significantly worse prognosis when 30 or 35 years of age was used

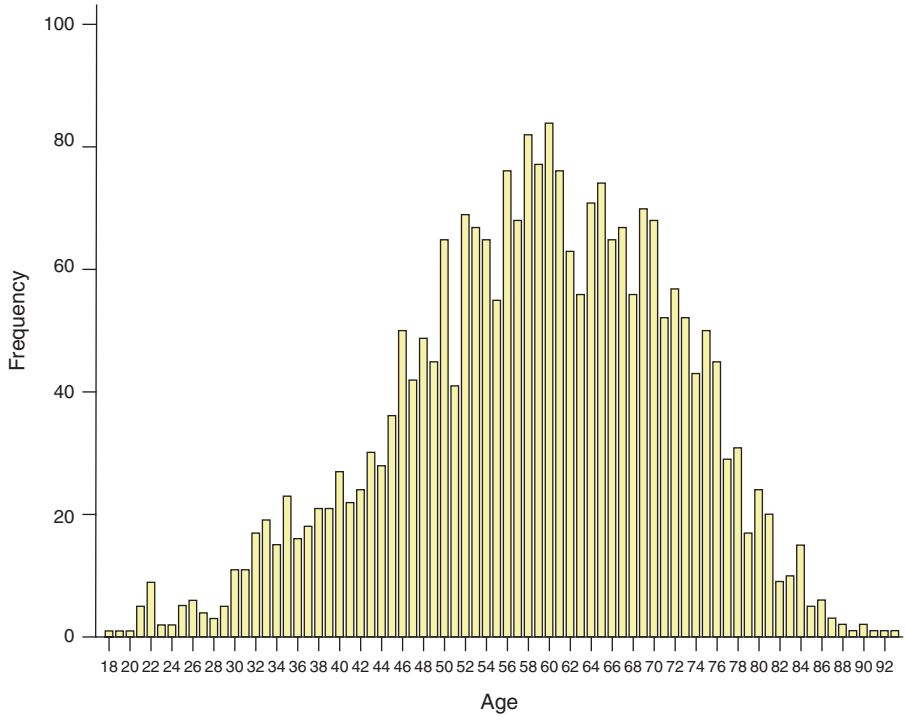
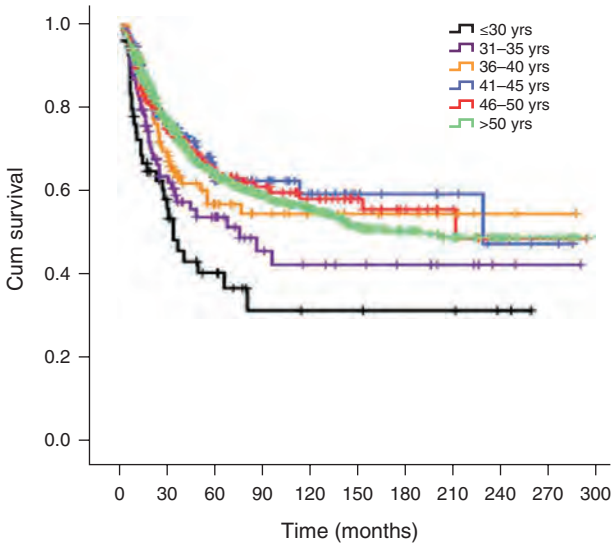


FIGURE 1. The distribution of patients' ages at the time of diagnosis as colorectal cancers.



Number at risk

≤30 yrs	55	24	14	6	5	5	4	4	3	--	--
31–35 yrs	85	43	27	15	12	10	8	5	3	1	--
36–40 yrs	103	60	32	21	18	12	9	6	2	1	--
41–45 yrs	139	86	47	29	19	11	8	6	4	2	--
46–50 yrs	250	134	85	49	38	25	17	9	5	3	1
>60 yrs	1825	994	559	320	218	140	95	53	32	13	1

FIGURE 2. The OS in 6 age groups (≤30, 31–35, 36–40, 41–45, 46–50, and >50 years old). The younger age groups (≤30 and 31–35 years old) were separated from the other groups. OS = overall survival.

as the cutoff, whereas the prognosis was not statistically worse when 40, 45, or 50 years of age was used as the cutoff. Therefore, 35 years old was considered the cutoff age for defining young adult colorectal cancer. Therefore, patients ≤35 years comprised the young adult group, while patients >35 years comprised the older group.

There were 140 cases (5.7%) and 2320 cases (94.3%) in young adult group and the older group, respectively (Table 1). The ratio of males to females in the young adult group was 1.1:1 and 1.4:1 in the older group. The percentages of colonic cancer, mucinous cancer, well differentiated type, poorly differentiated type, and stage III–IV were 52.9%, 30.7%, 10.7%, 44.3%, and 69.3%, respectively, in the young adult group and 53.8%, 17.4%, 21.1%, 19.7%, and 46.4%, respectively, in the older group, and the differences were statistically significant ($P = 0.019$, 0.000, 0.003, 0.000, and 0.000, respectively).

Regarding the impact of age on outcome, univariate analyses indicated that the young adult group had worse outcome compared with older group (relative risk [RR] = 1.728, $P = 0.000$). The 5- and 10-year OS were 48.9% and 38.6%, respectively, in the young adult group and 63.6% and 56.9%, respectively, in the older group (Figure 3). Stage-to-stage analysis showed that survival was similar between the young adult and older groups in the stage 0–III subgroup ($P = 0.640$, 0.825, 0.764, and 0.361, respectively) (see Appendix, Supplemental Digital Content 2, Subgroup analysis, http://links.lww.com/MD/A73). However, only in the stage IV subgroup was young age a predictor of worse prognosis of colorectal cancer ($P = 0.046$). In the multivariate analysis, after adjusting for covariates, including stage, tumor location, histological type, differentiation grade, and surgical approach, age was not an independent factor for the prognosis of colorectal cancer (RR = 0.811, $P = 0.105$). However, after adjusting for stage only, the RR of death in the young adult group was 1.276 (95% confidence interval [CI] 0.997–1.633), which was no longer significantly different ($P = 0.053$) (see Figure 4 and Appendix, Supplemental Digital Content 2, Subgroup analysis, http://links.lww.com/MD/A73). While adjusting for histological type, differentiation grade, and surgical approach, the RRs of death in the young adult group were higher at 1.599 (95% CI 1.246–2.051), 1.466 (95% CI 1.145–1.879), and 1.732 (95% CI 1.353–2.217), respectively (see Appendix, Supplemental Digital Content 3, Adjustment analyses, http://links.lww.com/MD/A73).

In the univariate analysis, other factors including histological type, differentiation grade, stage and surgical approach were correlated with OS ($P = 0.000$ for all), except for gender and tumor sites, which had P values of 0.271 and 0.160, respectively (see Appendix, Supplemental Digital Content 4, Univariate analysis, http://links.lww.com/MD/A73). In the multivariate analysis, factors including stage, surgical approach, differentiation grade and histological type were independent prognostic factors (see Table 2 and see Appendix, Supplemental Digital Content 5, The best Cox model to explore prognostic predictor, http://links.lww.com/MD/A73). As for the histological type, papillary cancer had a similar prognosis to mucinous cancer ($P = 0.129$).

DISCUSSION

Many studies showed have shown that colorectal cancer in young adults is heterogeneous. The definition of young age remains unclear; therefore, comparisons between studies cannot be performed directly. In previously published studies, 30, 40, 45, and 50 years of age have been used as cutoff ages.[19] Unfortunately, few studies have explored a suitable cutoff age based on a rational analysis. It may be reasonable to explore a suitable cutoff age according to epidemiological conditions of colorectal cancer. In this study, based upon the diagrams of age distribution and the survival curves of the different groups in the subgroup analysis, 35 years of age was determined to be a suitable cutoff age in our study. The proportion of young adults with colorectal cancer varied widely.[19] In prior studies, the percentage of young adults with colorectal cancer was 2.4% when 40 years old was used as the cutoff age and 3.1% when 45 years old was used as the cutoff age in western countries.[20,21] Additionally, the percentage of young adults with colorectal cancer was between 3.0% and 5.1% when 40 years old was used as the cutoff age in Asia.[12,15] In our study, 5.7% of the total patients were ≤35 years old. The median age of patients with colorectal cancer in China was much younger than that in western countries. It was suggested that developing colorectal cancer at a young age is related to race. A higher proportion of young adults with colorectal cancer was found in Asian countries, and the age of diagnosis tends to be much younger in China. Therefore, it is unreasonable to adopt the western criteria of using 40 or 50 years old as the cutoff age for our study, and it is necessary to find a more suitable cutoff age based on the epidemiology in special regions. Thus far, there have been few studies addressing the definition of young patient with colorectal cancer. Many studies have arbitrarily selected a cutoff age without explaining their rationale. This study was the first to explore the best cutoff age in a specific region, although the accuracy of the methods used needs to be further validated.

TABLE 1. Clinical and Pathologic Characteristics of Colorectal Cancer in Young Adult Group and Older Group, n (%)

Variance	Young Adult Group (n) (%)	Older Group (n) (%)	*P*
Total	140 (5.7)	2320 (94.3)	
Gender			NS
Male	74 (52.9)	1362 (58.7)	
Female	66 (47.1)	958 (41.3)	
Tumor location			0.019
Colon	61 (43.6)	1247 (53.8)	
Rectum	79 (56.4)	1073 (46.2)	
Histological type			0.000
Mucinous	43 (30.7)	404 (17.4)	0.000
Signet ring cell	7 (5.0)	21 (0.9)	0.002
Papillary	15 (10.7)	241 (10.4)	NS
Tubular	65 (46.5)	1549 (66.8)	0.000
Undifferentiated	8 (5.7)	52 (2.2)	0.019
Unclassified	2 (1.4)	53 (2.3)	NS
Differentiated grade			0.000
Well	15 (10.7)	490 (21.1)	0.003
Moderately	55 (39.3)	1224 (52.8)	0.002
Poorly	62 (44.3)	458 (19.7)	0.000
Unknown	8 (5.7)	148 (6.4)	NS
Stage T			0.032
Tis	2 (1.4)	34 (1.5)	NS
T1	3 (2.1)	97 (4.2)	NS
T2	9 (6.4)	369 (15.9)	0.003
T3	65 (46.5)	987 (42.5)	NS
T4	61 (43.6)	827 (35.6)	0.058
Tx	0 (0)	6 (0.3)	NS
Stage N			0.000
0	43 (30.7)	1268 (54.7)	0.000
1	41 (29.3)	589 (23.4)	NS
2	42 (30)	363 (15.6)	0.000
Nx	14 (10)	100 (4.3)	0.002
Stage M			0.000
M0	106 (75.7)	2032 (87.6)	
M1	34 (24.3)	288 (12.4)	
Stage TNM			0.000
0	2 (1.4)	34 (1.5)	NS
I	6 (4.3)	382 (16.5)	0.000
II	35 (25.0)	828 (35.7)	0.010
III	62 (44.3)	787 (33.9)	0.010
IV	35 (25.0)	289 (12.4)	0.000
Approach of surgery			0.040
R0	88 (62.9)	1484 (64.0)	NS
R1	43 (30.7)	781 (33.6)	NS
R2	9 (6.4)	55 (2.4)	0.009

NS = nonsignificance, Tis = tumor in situ.

There is much debate regarding the outcome of young patients with colorectal cancer. A study in 1990 showed that the overall crude and relative 5-year survival rates for young patients (≤40 years old) were both 60% but were 42% and 53% for old patients (>40 years old).[22] The 10-year survival rates were also higher in young adult patients. The better survival rates in young adults with colorectal cancer may be because of more effective treatments, such as adjuvant chemotherapy. Many studies have shown that young adults with colorectal cancer have similar outcomes as older patients with colorectal cancer.[12,15,20,21] In a study by Yeo et al,[12] 2426 patients from Singapore General Hospital from 2000 to 2005 were divided into 3 groups: ≤40, 41 to 50, and >50 years old. The results showed that there was no difference among their cancer-specific survivals. They concluded that young patients with colorectal cancer do not have a worse prognosis.

In our study, the 5- and 10-year OS rates were 48.9% and 38.6%, respectively, in the young adult group (≤35 years old) compared with 63.6% and 56.9%, respectively, in the older group. Young patients did have a worse survival (RR = 1.728, $P = 0.000$). However, the multivariate analysis showed that age was not an independent factor for prognosis. Therefore, a

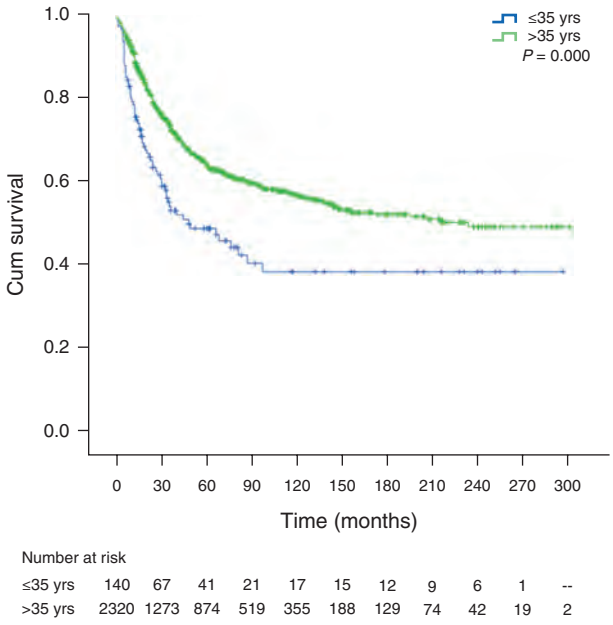


FIGURE 3. The OS of patients in the young adult group (≤35 years old) and the older group (>35 years old). The 5-year OS and 10-year OS were 48.9% and 38.6%, respectively, in the young adult group and 63.6% and 56.9%, respectively, in the older group ($P = 0.000$). OS = overall survival.

detailed procedure was used to explore the impact of age on prognosis. As listed above, the young adult group had a higher percentage of stage III–IV patients, whereas the older group had a higher percentage of stage I–II patients. The significant difference in outcome between the 2 groups was no longer present when the analysis was adjusted by stage but still existed when the analysis was adjusted by other covariates. For that reason, we conclude that age is correlated with colorectal cancer stage, which results in a worse prognosis. The results appeared

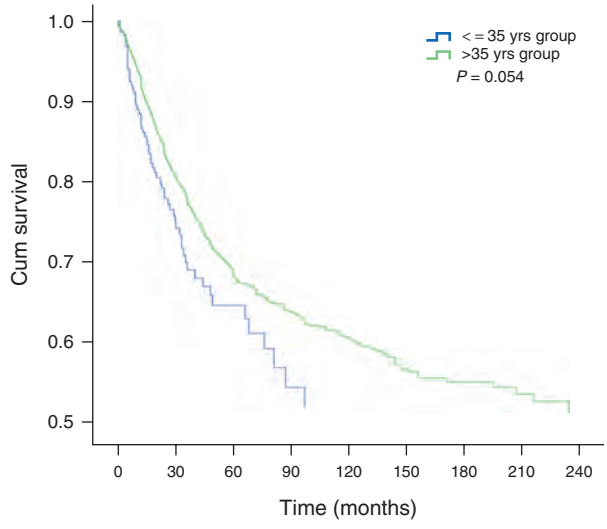


FIGURE 4. The OS in the young adult group and the older group was not significantly different after adjusting for stage ($P = 0.054$). OS = overall survival.

to be consistent with the analysis of the surveillance epidemiology and end results population database by O'Connell et al.[11] Specifically, younger patients with colorectal cancer had worse survival rates because they presented with more advanced stage disease. In clinical practice, young patients presenting with changes in bowel habits, constipation, diarrhea, blood in their stool, and abdominal discomfort should be evaluated for colorectal cancer to enable and achieve an earlier diagnosis.[13,23] Early detection may be the best way to improve their prognosis.

In our study, the stratified analysis showed that the young adult patients with colorectal cancer had a similar prognosis to the older patients in the stage I–III subgroup. A study by Quah et al also confirmed that when stage was analyzed, young patients fared as well as the older patients with stage I–III colorectal cancer.[24] In our stage-to-stage analysis, patients with stage II tumors had better outcomes conceivably because they received adjuvant chemotherapy. A study conducted by O'Connell et al also showed that survival was significantly better for young patients with stage II disease (88.6% vs 82.7%, $P = 0.01$), was worse for patients with stage IV disease, and was similar for patients with stage I and III disease. As for stage II colon cancer, a pooled analysis of randomized control trials showed that only patients with risk factors could achieve better survival from adjuvant chemotherapy.[25] Furthermore, the study of the Quick And Simple And Reliable collaborative group indicated that adjuvant chemotherapy improved the survival of patients with stage II colorectal cancer, but the treatment efficacy did not differ by age.[26] In clinical practice, young patients often receive excessive medical treatment. Our study showed that young age should not be considered a risk factor for stage II colorectal cancer.

The present study had some limitations. First, the clinical data did not include the signs and symptoms experienced by the colorectal cancer patients. It was impossible to identify alarming symptoms in young patients and make an early diagnosis. Second, the number of patients with detailed records of their adjuvant treatment regimen in our system was 618 (25.1%), in which 49 were from the young adult group (36 cases accepted adjuvant chemotherapy) and 569 were from the older group (426 cases accepted adjuvant chemotherapy). Many patients treated between 1980 and 1990 did not receive adjuvant chemotherapy or radiotherapy. In addition, many patients that had surgery at our institution received their adjuvant treatment at other institutions, making it difficult to collect complete treatment data. Additionally, chemotherapy regimens have changed over the past 30 years. Because of the missing data and variations in chemotherapy regimens, it was difficult to analyze the impact of treatment on outcome. Therefore, treatment was not included in the multivariate analysis. Third, some of the unresectable patients who did not receive palliative surgery were not included in our analysis; consequently, the conclusions regarding the stage IV subgroup may have been biased. The pathogenesis of young colorectal cancer was not explored in depth to confirm if carcinogenesis was an independent prognostic factor for older patients with colorectal cancer.

To our knowledge, this is the largest study on colorectal cancer from a single center in China. Under the Chinese medical care system, it is difficult to perform a valid study with a long follow-up time. In this study, we collected and analyzed data from 30 years' follow-up, which provided information on the present state of diagnosis and treatment for colorectal cancer in China. This study is the first to explore the definition of young patients with colorectal cancer in a specific region. The results

TABLE 2. Univariate and Multivariate Analysis (Cox Proportional Hazard Model) of Prognostic Factors for 2460 Patients With Colorectal Cancer

	Univariate Analysis			Multivariate Analysis		
	RR	95% CI	*P*	RR	95% CI	*P*
Age (>35 /≤35years)	0.579	0.453–0.740	0.000	0.811	0.629–1.045	0.105
Stage (IV/III/II/I)	2.855	2.640–3.154	0.000	2.457	2.229–2.709	0.000
Approach of surgery (R2/ R1/R0)	2.678	2.357–3.041	0.000	1.539	1.338–1.770	0.000
Differentiated type*			0.000			0.000
Moderately	1.116	0.917–1.359	0.273	0.992	0.813–1.212	0.941
Poorly	2.217	1.799–2.734	0.000	1.596	1.250–2.038	0.000
Unknown	1.283	0.935–1.762	0.123	1.111	0.796–1.551	0.535
Histological type†			0.000			0.009
Signet ring cell	1.973	1.212–3.212	0.006	1.336	0.816–2.187	0.250
Papillary	0.827	0.647–1.057	0.129	1.425	1.089–1.864	0.010
Tubular	0.747	0.624–0.895	0.002	1.116	0.907–1.374	0.299
Undifferentiated	1.044	0.663–1.646	0.852	0.805	0.508–1.276	0.355
Unclassified	0.670	0.416–1.079	0.100	2.111	1.270–3.508	0.004
Tumor location (rectum/colon)	1.105	0.961–1.270	0.161	1.195	1.038–1.376	0.013
Gender (female/male)	1.082	0.904–1.246	0.273			

CI = confident interval, RR = relative risk.
* Reference group is well.
† Reference group is mucinous cancer.

of this study may serve as a reference for future studies or colorectal screening.

CONCLUSION

In conclusion, 35 years old was a suitable cutoff age for defining young adults with colorectal cancer. Expect special clinical characteristics, young adult patients with colorectal cancer had worse prognosis, primarily because they often presented with advanced stage tumors, such as stage III and IV tumors. When excluding the impact of tumor stage, age was not considered an independent factor for prognosis. When a stage-to-stage analysis was performed, it indicated that young adult patients with colorectal cancer had a worse outcome but only if their tumors were stage IV.

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