Young Patients With Colorectal Cancer Have Higher Early Mortality but Better Long-Term Survival

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INTRODUCTION: **To define the prognosis of colorectal cancer (CRC) in young patients and to compare their postoperative treatment with that of older patients.**

METHODS: **This multicenter study enrolled 5,457 patients with primary CRC who underwent surgical resection. The overall survival (OS), clinicopathologic characteristics, and postoperative treatment of 253 young patients aged 18–44 years and 5,204 older patients aged 44–80 years were analyzed.**

RESULTS: **The OS rate was 77.1% for young and 74.2% for older patients ($P = 0.348$). Landmark analysis showed a significant difference in survival between young and older patients, with 63.8% of deaths among young patients being within 25 months of surgery compared with 42.4% among older patients ($P = 0.002$). Among those who survived more than 25 months, young patients had significantly better survival than older patients ($P = 0.009$). Multivariable analysis of young patients revealed that the tumor location, perineural invasion, and stage were associated with poor survival within 25 months; after this period, stage was the only prognostic marker. Young patients were more likely to receive chemotherapy, particularly multiagent regimens. For young patients, no significant difference in OS was found based on the chemotherapy regimen, regardless of disease stage (II, III, or IV, all $P > 0.05$). In addition, unlike in older patients, no difference in OS was found in young patients regardless of the drug regimen administered (all $P > 0.05$).**

DISCUSSION: **Young-onset CRC may have a unique disease biology that warrants further research and therapy development.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A888

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INTRODUCTION

Colorectal cancer (CRC) is the third leading cause of cancer-related death (1). While the incidence of patients with CRC aged 50 years and older has decreased over the past few decades, there seems to be an opposite trend among younger patients in a substantial number of countries (2–5). The latest recommendations from the US Preventive Services Task Force lowered the age for initiating average-risk CRC screening from 50 years to 45 years (6). Although a proportion of young-onset CRC can be attributed to hereditary syndromes, most are sporadic rather than familial (7,8). Multiple studies have shown that CRC in young patients has a distinctive biologic phenotype that differs from that in old patients (9,10). Age at diagnosis is not considered in modern treatment strategies, and young patients are often not clinically suspected of having CRC, leading to incorrect management early in their disease course. Thus, it is essential for clinicians to be aware of the rising incidence of young-onset CRC.

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The prognosis of young-onset CRC has been poorly described, with conflicting results being reported by a limited number of survival studies. The results of some studies have suggested that young patients have worse survival outcomes (11–16), while others suggest that they have similar or better survival outcomes than older patients (15,17–21). Radical surgical resection remains the primary treatment of both young and old patients with CRC. However, research focusing on postoperative treatment and the associated outcomes is very sparse. Because of the poor prognosis and conflicting results reported for young patients, the oncotherapeutic sensitivity of this patient population remains unclear, making it difficult to advise them about chemotherapy options. According to the World Health Organization classification, those aged 44 years or younger were defined as younger, and few previous studies have investigated the characteristics of young-onset CRC with the cutoff age of 44 years (22–25).

In this article, we aimed to define the survival of young patients with CRC (age range: 18 years to 44 years or younger) compared with that of old patients (age range: 44 years or older to 80 years or younger) using landmark analysis and to explore the influence of chemotherapy on survival outcomes.

METHODS

Study population

This multicenter study was based on a prospectively maintained CRC database from 3 hospitals (Tianjin Union Medicine Center, Tianjin Third Central Hospital, and Wuhan Tongji Hospital). We reviewed the electronic medical records of all patients with histologically confirmed primary CRC who underwent curative resection between January 2012 and December 2017. All patients were followed up until the last contact or death occurred. The survival status and cause of death were obtained from the medical records or death certificates. The end of the follow-up period was October 31, 2021. All patients signed informed consent forms before receiving treatment. This study was approved by the Ethics Committee of Tianjin Union Medicine Center.

In this study, a total of 253 patients with CRC aged 18–44 years constituted the young-onset group. The comparative group with later-onset CRC consisted of 5,204 patients older than 44 years but aged 80 years or younger at diagnosis. Patients younger than 18 years and patients older than 80 years were excluded to minimize bias. In addition, patients with known familial adenomatous polyposis, inflammatory bowel disease, and hereditary nonpolyposis CRC (Lynch syndrome [LS]) were excluded. Patients with carcinoma *in situ* and those with histological types such as gastrointestinal stromal and neuroendocrine tumors were also excluded.

Outcomes and definitions

Our primary outcome was overall survival (OS), defined as the interval from the date of surgery to the date of death due to CRC or the date of last contact. Patients who died from any other cause were excluded. Our secondary outcome was the proportion of deaths occurring within 25 months (including 25 months) from surgery among the total deaths.

The Tumour, node, and metastasis stage was determined according to the American Joint Committee on Cancer staging system. In this study, high-risk stage II disease was defined as T4 stage, poorly differentiated histology, perineural invasion positivity, venous invasion positivity, and mismatch repair (MMR) proficiency (26). The right colon was defined as proximal to the splenic flexure, whereas the left colon was defined as from the splenic flexure to the rectosigmoid junction.

Statistical analysis

Chi-square tests or the Fisher exact test was used to compare categorical variables between younger and older patients. A multivariable logistic regression model was performed to assess the association between age and the receipt of postoperative chemotherapy, adjusting for potential confounders, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. In addition, a multivariate Cox regression model was performed to assess the association between the variables showing statistical significance in the univariate analysis and OS within vs after 25 months of operation, with hazard ratios (HRs) and 95% CIs calculated. Forest plots were generated to visualize the results of the multivariate Cox analysis. The Benjamini-Hochberg test was used to correct P values for multiple comparisons.

OS curves were generated using Kaplan-Meier (K-M) estimates. A key assumption in Cox regression is that the ratio of hazard functions does not vary with time, known as the proportional hazard (PH) assumption (27). We checked the fulfillment of the PH assumption for our Cox regression model using the Schoenfeld residuals test and found that the test for age rejected the PH assumption ($P = 0.0017$). Thus, the landmark analysis was a more appropriate approach. Consistent result was found with the use of each cutoff time point from 23 to 26 months, however, to achieve the best balance between the prelandmark and postlandmark parts, 25 months was finally identified as the cutoff point. Therefore, landmark analysis was performed for events from surgery up to 25 months and from 25 months to the final end point to assess the time-dependent survival of younger vs older patients.

All analyses were performed using R software (V.4.1.2), and landmark analysis was conducted using "jskm" package. Two-sided P values <0.05 were considered to be statistically significant.

RESULTS

Clinical characteristics of CRC in young and older patients

Table 1 summarizes the distributions of clinical characteristics by age (Table 1). Of all patients enrolled in this study (n = 5,457), the median age was 62.5 years (range: 18–80 years), and 253 (4.6%) were diagnosed between 18 and 44 years of age. A total of 54.5% of younger patients with CRC and 58.4% of older patients with CRC were men.

Compared with their older counterparts, younger patients with CRC were more likely to have poorly differentiated tumors ($P = 0.009$), vascular invasion ($P = 0.025$), and MMR deficiency ($P < 0.001$). In addition, nodal or distant metastases at diagnosis were present more frequently in younger patients than in older patients. A total of 38.7% and 8.7% of the young group had stage III and stage IV disease, respectively, while 36.9% and 6.1% of the older group had stage III and stage IV disease, although this difference was not statistically significant ($P = 0.286$). Among the patients with available information on tumor location, 56.4% and 26.4% of young patients presented with left colon and rectal tumors, respectively, which was slightly higher than that of older patients (55.3% and 23.6%, respectively, $P = 0.286$).

Regarding postoperative chemotherapy, more young patients received chemotherapy (67.6% vs 53.0%, $P < 0.001$) and radiotherapy (12.3% vs 6.6%, $P < 0.001$) and multiagent therapy

Table 1. Clinical characteristics and treatments of patients by age at diagnosis

Characteristic	Overall (n = 5,457)	Colorectal cancer		
		18–44 yr (n = 253)	44–80 yr (n = 5,204)	*P* value[a]
Sex, n (%)				
Female	2,281 (41.8)	115 (45.5)	2,166 (41.6)	0.286
Male	3,176 (58.2)	138 (54.5)	3,038 (58.4)	
TNM stage at diagnosis, n (%)				
Stage I	837 (15.3)	31 (12.3)	806 (15.5)	0.286
Stage II	2,264 (41.5)	102 (40.3)	2,162 (41.5)	
Stage III	2,019 (37.0)	98 (38.7)	1,921 (36.9)	
Stage IV	337 (6.2)	22 (8.7)	315 (6.1)	
Location, n (%)				
Rectum	3,005 (55.1)	141 (55.7)	2,864 (55.0)	0.286
Left colon	1,289 (23.6)	66 (26.1)	1,223 (23.5)	
Right colon	1,131 (20.7)	43 (17.0)	1,088 (20.9)	
Unspecified	32 (0.6)	3 (1.2)	29 (0.6)	
Pathological grade, n (%)				
Well/moderately differentiated	4,132 (75.7)	171 (67.6)	3,961 (76.1)	0.009
Poor differentiated	755 (13.8)	42 (16.6)	713 (13.7)	
Special types[b]	454 (8.3)	33 (13.0)	421 (8.1)	
Unknown	116 (2.1)	7 (2.8)	109 (2.1)	
Vascular invasion, n (%)				
No	4,715 (86.4)	205 (81.0)	4,510 (86.7)	0.025
Yes	742 (13.6)	48 (19.0)	694 (13.3)	
Perineural invasion, n (%)				
No	4,944 (90.6)	224 (88.5)	4,720 (90.7)	0.298
Yes	513 (9.4)	29 (11.5)	484 (9.3)	
MMR status, n (%)				
MMR deficient	643 (11.8)	57 (22.5)	586 (11.3)	<0.001
MMR proficient	2,802 (51.3)	115 (45.5)	2,687 (51.6)	
Unknown	2,012 (36.9)	81 (32.0)	1,931 (37.1)	
Postoperative chemotherapy, n (%)				
No	2,244 (41.1)	60 (23.7)	2,184 (42.0)	<0.001
Yes	2,893 (53.0)	171 (67.6)	2,722 (52.3)	
Single agent[c]	382 (7.0)	10 (4.0)	372 (7.1)	
Multiagent	2,424 (44.4)	155 (61.3)	2,269 (43.6)	
FOLFOX	1,671 (30.6)	102 (40.3)	1,569 (30.1)	
CAPEOX	357 (6.5)	29 (11.5)	328 (6.3)	
FOLFIRI	396 (7.3)	24 (9.5)	372 (7.1)	
Regimen unknown	87 (1.6)	6 (2.3)	81 (1.5)	
Chemotherapy unknown	320 (5.9)	22 (8.7)	298 (5.7)	
Postoperative radiotherapy, n (%)				
Yes	374 (6.9)	31 (12.3)	343 (6.6)	<0.001
No	2,069 (37.9)	78 (30.8)	1,991 (38.3)	
Unknown	3,014 (55.2)	144 (56.9)	2,870 (55.1)	

MMR, mismatch repair; TNM, tumour, node, and metastasis.
[a]*P* values were corrected using the Benjamini-Hochberg method.
[b]Special types include mucinous adenocarcinoma, signet-ring cell carcinoma, and squamous cell carcinoma.
[c]Single agent refers to capecitabine or 5-fluorouracil based.

(61.3% vs 44.4%, $P = 0.009$) than older patients. Differences were also observed for regimen selection. FOLFOX was administered to the majority of both young and old patients. The proportion of young patients who received CAPEOX or FOLFIRI was similar to that of older patients, while FOLFIRI was more frequently administered than CAPEOX in older patients.

Survival analysis of CRC in young and older patients

The median follow-up interval was 5.1 years (interquartile range, 3.3–6.5 years). Figure 1a presents OS according to landmark analysis at the 25-month break point. Younger patients experienced an obvious survival disadvantage compared with older patients before the landmark time point, that is, during the first 25 months after surgery (HR = 1.35, 95% CI = 0.52–1.02, $P = 0.042$). Their OS outcomes after 25 months, however, were significantly better than those of older patients (HR = 0.57, 95% CI = 1.13–2.69, $P = 0.009$). By contrast, in the stage-specific analysis, only young patients with stage II disease had a more favorable long-term prognosis than older patients (HR = 0.34, 95% CI = 1.06–7.68, $P = 0.026$) (see Supplementary Figure S1a–d, Supplementary Digital Content 1, http://links.lww.com/CTG/A888). Figure 1b presents a naïve K-M plot, revealing that the OS in young patients was slightly lower than that in old patients over a short term but then showed an improving trend after approximately 3 years (Figure 1b). However, this plot does not indicate a statistically significant difference after the log-rank test was performed ($P = 0.491$). Similarly intersecting K-M curves were also reported in previous studies relative to young-onset CRC (11,19,22); thus, interpretation of a single summary value of HR from Cox regression may not be appropriate, and further analysis is needed.

Young patients had a slightly superior OS advantage over older patients (77.1% vs 74.2%, $P = 0.348$) (Figure 1c), and this advantage was consistent across all stages (stage I: 96.8% vs 92.1%, $P = 0.535$; stage II: 92.2% vs 84.9%, $P = 0.061$; and stage III: 69.4% vs 64.1%, $P = 0.336$, except for stage IV (13.6% vs 17.1%, $P = 0.897$). However, we found that young patients were more likely to die during the first 25 months of surgery (63.8% vs 42.4%, $P = 0.002$) (Figure 1d). In the stage-specific analyses, 50.0%, 56.7%, and 84.2% of the deaths in young patients with stage II, III, and IV CRC, respectively, occurred within 25 months, while those proportions in older patients were 23.6%, 43.6%, and 70.5%, respectively.

The results of the multivariate Cox analysis for OS in young and old patients are presented as forest plots (see Supplementary Figure S2, Supplementary Digital Content 1, http://links.lww.com/CTG/A888). For young patients, tumour, node, and metastasis stage was the strongest independent predictor (HR = 5.82, $P < 0.001$), and right-sided colon tumors and MMR proficiency were also associated with poor survival (HR = 3.13, $P = 0.034$; HR = 3.58, $P = 0.024$, respectively). Nevertheless, the association for location and MMR was no longer significant

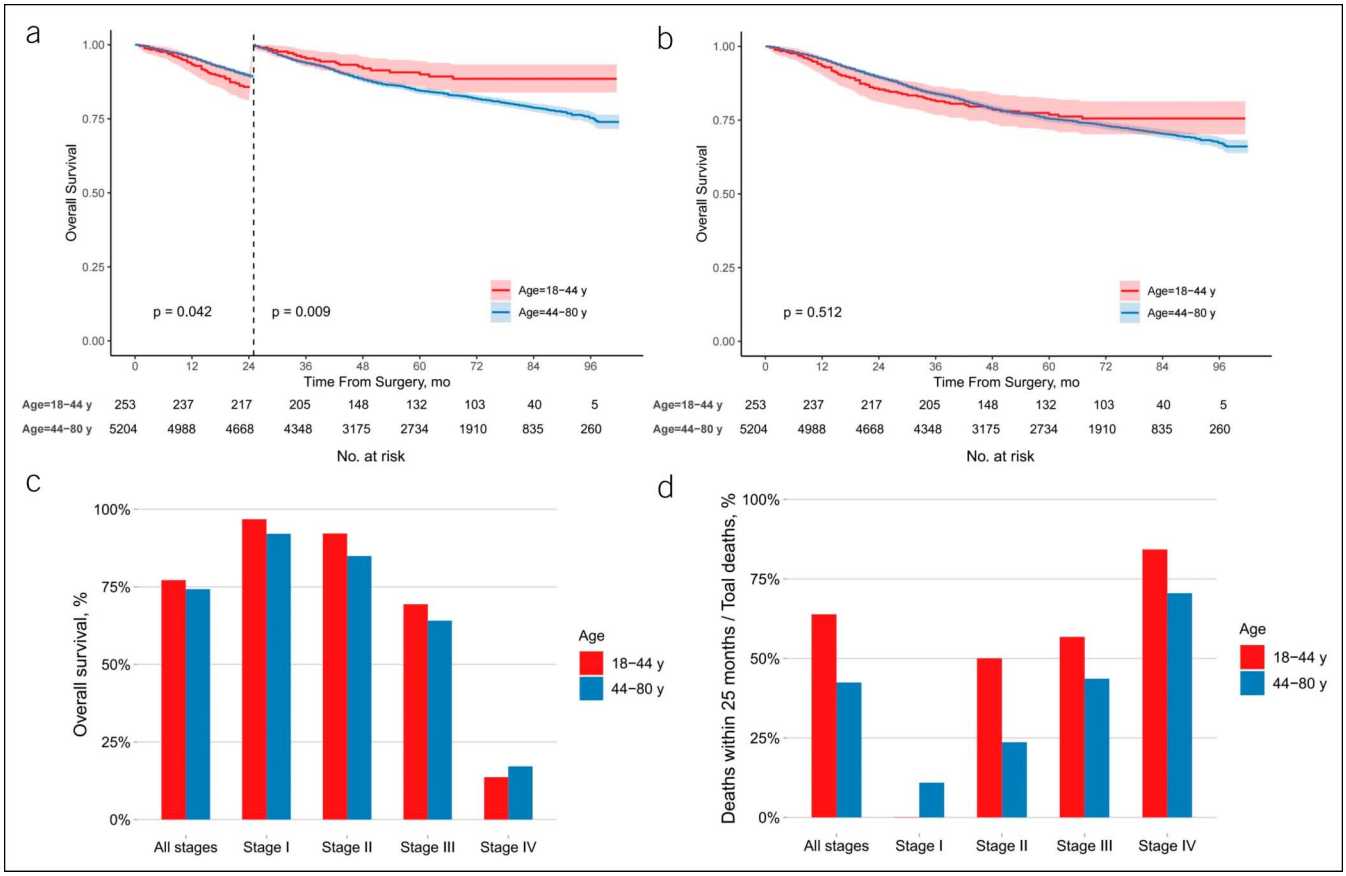

Figure 1. (**a**) Landmark analysis of OS with a breakpoint at 25 months after surgery for young patients aged 18–44 years vs older patients aged 44–80 years. (**b**) Naïve Kaplan-Meier estimates of OS for young vs older patients. (**c**) OS rate stratified by age and tumor stage. (**d**) Proportion of deaths within 25 months of surgery to total deaths stratified by age and tumor stage. OS, overall survival.

after the Benjamini-Hochberg correction. For older patients, all clinical parameters, including sex, perineural invasion, vascular invasion, location, tumor differentiation, MMR, and stage, had adverse effects on survival (all $P < 0.05$), with the effect of MMR less significant after correction.

Additional Cox analyses of OS before vs after 25 months were performed for the young patient group (see Supplementary Table S1, Supplementary Digital Content 1, http://links.lww.com/CTG/A888). Multivariable analysis revealed that stage III–IV disease was the most significant factor associated with poor survival from the time of surgery up to 25 months in young patients (HR = 8.54, $P < 0.001$), followed by location (HR = 2.74, $P = 0.025$) and perineural invasion (HR = 2.48, $P = 0.035$). After 25 months, stage seemed to be the only significant prognostic marker for young patients (HR = 4.81, $P = 0.002$).

When the old group was further subdivided into 44–60, 60–70, and 70–80 years group, younger patients had a more favorable survival: for patients aged 44–60, 60–70, and 70–80 years, the OS was 78.5%, 75.4%, and 66.7%, respectively (Table 2). Meanwhile, younger patients within the old group also had a better short-term survival, according to the smaller proportion of deaths within 25 months (40.7%, 42.7%, and 43.6%, respectively), which may serve as an additional evidence for the distinctive survival pattern of young-onset CRC. As summarized in Table 2, patients aged 18–44 years had a higher early mortality than each subgroup of old patients, although the OS was similar to the youngest 44–60 years subgroup (77.1% vs 78.5%, $P = 0.598$). This unique trend might suggest a distinctive pathogenesis in patients with young-onset CRC; further investigation is needed.

Postoperative treatment regimens for young and old patients and the associated outcomes

After adjusting for potential confounders, young patients were much more likely to receive postoperative chemotherapy than older patients (OR = 2.36, $P < 0.001$), which was consistent across all stages. All adjusted ORs are summarized in Table 3, except for stage IV, in which the number of young patients was too limited to calculate an OR value (Table 3). Moreover, among patients who received chemotherapy, young patients were more likely to receive multiagent therapy (OR = 2.59, $P = 0.014$).

In stage I and low-risk stage II, young patients had similar OS outcomes regardless of whether they received postoperative chemotherapy (all $P > 0.05$) (see Supplementary Figure S3a,b, Supplementary Digital Content 1, http://links.lww.com/CTG/A888), which was consistent with that found for older patients (all $P > 0.05$) (see Supplementary Figure S3c,d, Supplementary Digital Content 1, http://links.lww.com/CTG/A888).

Survival differences were observed between different age groups of high-risk stage II patients, and these differences persisted from stage II to stage IV. The survival outcomes of young patients who received chemotherapy remained similar to those of young patients who did not receive chemotherapy within the same stage (all $P > 0.05$) (Figure 2a–c and Supplementary Figure S3e, Supplementary Digital Content 1, http://links.lww.com/CTG/A888), while older patients significantly benefited from receiving chemotherapy ($P = 0.001$ for high-risk stage II; $P = 0.001$ for stage II; $P = 0.001$ for stage III; and $P = 0.015$ for stage IV) (Figure 2d–f and see Supplementary Figure S3f, Supplementary Digital Content 1, http://links.lww.com/CTG/A888). This suggests the need to consider applying the present guidelines for adjuvant chemotherapy to young patients with CRC.

Next, we stratified patients who received chemotherapy based on the regimen administered. The proportions of specific chemotherapy regimens administered to stage II, III, and IV patients are presented in Figure 2g. For young patients, no significant difference in OS was found based on the regimen, regardless of disease stage (II, III, or IV, all $P > 0.05$) (see Supplementary Figure S4a–c, Supplementary Digital Content 1, http://links.lww.com/CTG/A888). For older patients, FOLFOX resulted in more favorable survival outcomes than CAPEOX ($P = 0.021$), FOLFIRI ($P = 0.002$), and single-agent therapy ($P = 0.043$), but only for those with stage II disease (see Supplementary Figure S4d, Supplementary Digital Content 1, http://links.lww.com/CTG/A888). However, for those with stage III disease, the survival difference between FOLFOX and CAPEOX was not significant ($P = 0.904$), but FOLFOX still performed better than FOLFIRI ($P < 0.001$) and single-agent therapy ($P = 0.01$) (see Supplementary Figure S3e, Supplementary Digital Content 1, http://links.lww.com/CTG/A888). These advantages of FOLFOX and CAPEOX persisted in older patients with stage IV disease (FOLFOX vs CAPEOX, $P = 0.73$; FOLFOX vs FOLFIRI, $P = 0.06$; FOLFOX vs single-agent, $P = 0.03$) (see Supplementary Figure S4f, Supplementary Digital Content 1, http://links.lww.com/CTG/A888). Additional K-M plots for high-risk stage II patients (young vs old patients) stratified by regimen are shown in Supplementary Figure S5a-b (see Supplementary Digital Content 1, http://links.lww.com/CTG/A888).

DISCUSSION

Although CRC is believed to be less common in Asian countries than in Western countries, there is also an increasing trend of young-onset CRC in the Asian population, including China (28,29). In this study, 253/5,457 (4.6%) patients treated at our center comprised the young CRC group, which is considerably less than other reports from Asia, such as 10.1% in Taiwan (18), 13.4% in Sri Lanka (30), and 16.8% in Guangdong Province of China (22). This low percentage may be due to the CRC screening program that was implemented in Tianjin from 2012, resulting in a dramatic increase in the number of older patients diagnosed with CRC (31).

The prognosis of young-onset CRC remains controversial. In this study, the OS of young patients was found to be similar to that of older patients (77.1% vs 74.2%, $P = 0.348$), consistent with most previous studies. However, based on our clinical observations, we found that young patients were more likely to die within 1–3 years after surgery. Our results showed that young patients (aged 18–44 years) with CRC had a higher mortality rate within 25 months after surgery (63.8% vs 42.4%, $P = 0.002$) but a better long-term prognosis if they survived longer than 25 months compared with older patients (log-rank $P = 0.009$). The increased early mortality in young patients found in our study is consistent with that reported in previous studies. Ezzo et al. (14) revealed that 64% of young patients (younger than 40 years) died within 18 months postoperatively. A Sri Lankan study of 53 young patients with CRC (younger than 40 years) reported that 94% of young patient deaths occurred within 20 months of surgery (30). In addition, in some studies suggesting a similar or better survival for young patients with CRC vs older patients, an intersected K-M curve was observed, which implies that the PH assumption may not be satisfied, and therefore, interpretation of a single summary value of HR from traditional Cox regression may not be appropriate (27,32). For example, in the K-M plot for young (younger

Table 2. Comparison of OS and deaths within 25 months between young (ages 18–44 years) and old (ages 44–60, 60–70, and 70–80 years) patients with colorectal cancer

	OS			Deaths within 25 mo		
Age group	No. of patients	OS, %	HR (95% CI)[a]	No. of deaths	Proportion of deaths occurred within 25 mo, %	OR (95% CI)[b]
All stages						
Young group, yr						
18–44	253	77.1		58	63.8	
Old group, yr						
44–60	1,784	78.5	1 (Reference)	383	40.7	1 (Reference)
60–70	2,078	75.4	1.25 (1.09–1.42)	511	42.7	1.09 (0.83–1.42)
70–80	1,342	66.7	1.75 (1.52–2.01)	447	43.6	1.12 (0.85–1.48)
Stage I						
Young group, yr						
18–44	31	96.8		1	0	
Old group, yr						
44–60	279	95.7	1 (Reference)	12	0	NA[c]
60–70	324	92.6	1.76 (0.88–3.52)	24	12.5	
70–80	203	86.2	3.39 (1.71–6.69)	28	14.3	
Stage II						
Young group, yr						
18–44	102	92.2		8	50	
Old group, yr						
44–60	706	90.5	1 (Reference)	67	19.4	1 (Reference)
60–70	856	84.6	1.76 (1.30–2.37)	132	24.2	1.31 (0.64–2.72)
70–80	600	78.8	2.50 (1.85–3.39)	127	25.2	1.37 (0.66–2.83)
Stage III						
Young group, yr						
18–44	98	69.4		30	56.7	
Old group, yr						
44–60	696	68.4	1 (Reference)	220	36.8	1 (Reference)
60–70	778	67.0	1.15 (0.96–1.38)	257	44.7	1.39 (0.96–2.01)
70–80	447	52.3	1.75 (1.45–2.11)	213	49.3	1.67 (1.14–2.45)
Stage IV						
Young group, yr						
18–44	22	13.6		19	84.2	
Old group, yr						
44–60	103	18.4	1 (Reference)	84	73.8	1 (Reference)
60–70	120	18.3	1.03 (0.76–1.39)	98	69.4	0.80 (0.42–1.54)
70–80	92	14.1	0.98 (0.71–1.35)	79	68.4	0.77 (0.39–1.51)

CI, confidence interval; HR, hazard ratio; MMR, mismatch repair; NA, not applicable; OR, odds ratio; OS, overall survival.
[a]Multivariable Cox regression model adjusted for sex, differentiation grade, location, perineural invasion, vascular invasion, and MMR status.
[b]Multivariable logistic regression model adjusted for sex, differentiation grade, location, perineural invasion, vascular invasion, and MMR status.
[c]HR not calculable owing to 0 event in this subgroup.

than 45 years) and old patients with CRC reported by Yang et al. (22), there was an intersection at approximately 3 years, before which young patients had poor survival and after which young patients had better survival relative to old patients. This result was actually consistent with our findings. The same trend for young patients with CRC patients (younger than 40 years) was also observed in a study from the UK (11), with an intersection at approximately 30 months in the K-M plot, and in the results of a

Table 3. Likelihood of receiving postoperative chemotherapy and multiagent regimens for young (ages 18–44 years) and older (ages 44–80 years) patients with colorectal cancer

	Receiving postoperative chemotherapy			Multiagent regimens		
Stage	N (%)	OR (95% CI)[a]	*P* value[c]	N (%)	OR (95% CI)[a]	*P* value[c]
All stages						
44–80 yr	2,722 (55.5)	1 (Reference)		2,269 (85.9)	1 (Reference)	
18–44 yr	171 (73.4)	2.36 (1.71–3.25)	<0.001	155 (93.9)	2.59 (1.35–5.00)	0.014
Stage I						
44–80 yr	166 (21.8)	1 (Reference)		107 (68.2)		
18–44 yr	13 (50.0)	3.38 (1.49–7.66)	0.002	7 (63.6)	NA	0.757
Overall stage II						
44–80 yr	1,177 (55.1)	1 (Reference)		945 (82.4)	1 (Reference)	
18–44 yr	70 (72.2)	2.19 (1.39–3.44)	0.002	67 (97.1)	7.18 (1.75–29.55)	0.007
Low-risk stage II						
44–80 yr	777 (54.1)	1 (Reference)		632 (82.8)		
18–44 yr	39 (67.2)	1.78 (1.02–3.11)	0.008	37 (97.4)	7.66 (1.04–56.13)	0.042
High-risk stage II						
44–80 yr	400 (57.0)	1 (Reference)		313 (81.5)		
18–44 yr	31 (79.5)	2.98 (1.35–6.58)	0.008	30 (96.8)	6.68 (0.90–49.80)	0.048
Stage III						
44–80 yr	1,225 (71.1)	1 (Reference)		1,082 (91.4)		
18–44 yr	74 (84.1)	2.65 (1.39–5.06)	0.009	68 (95.8)	NA[b]	0.271
Stage IV						
44–80 yr	154 (54.0)			135 (88.2)		
18–44 yr	14 (63.6)	NA[b]	0.383	13 (92.9)	NA[b]	0.702

CI, confidence interval; MMR, mismatch repair; NA, not applicable; OR, odds ratio; TNM, tumour, node, and metastasis.
[a]Multivariable logistic regression model adjusted for sex, differentiation grade, TNM stage, location, perineural invasion, vascular invasion, and MMR status.
[b]Variables were not included in multivariable analysis.
[c]*P* values were corrected using the Benjamini-Hochberg method.

study from Eastern China (16). However, this trend was not described or further analyzed in other previous reports. Thus, we are the first to demonstrate this unique survival pattern in young-onset CRC with landmark analysis.

Currently, there is no defined cutoff age for young-onset CRC. Previous studies have used different definitions for young patients (i.e., 35, 40, 45, 50, or 55 years), which may partly explain the conflicting results across previous studies. Of importance, in most studies that defined the age cutoff as 45 years or younger, poorer short-term survival for young-onset patients with CRC was reported (11,14,30), or higher early mortality was observed in the survival plots (22). However, in most studies for which the age of young patients was cut off at 50 years or older, an opposite trend was reported (17,33–35). Therefore, based on our data, additional landmark analyses with cutoff ages of 40 and 50 years were performed (see Supplementary Figure S6a,b, Supplementary Digital Content 1, http://links.lww.com/CTG/A888). Significantly increased early mortality and better long-term survival were found in patients when the cutoff age was 40 years but not observed when the cutoff age was 50 years. The heterogeneity found when different cutoff ages were used suggests that the use of an arbitrary cutoff is a considerable limitation and that further age-based subgrouping for both young and old patients is needed.

Additional analyses were performed on patients with colon cancer and rectal cancer separately, and the results remained consistent with our findings. Young patients had a slightly higher OS (79.4% vs 75.8%, $P = 0.337$ for rectal cancer; 75.2% vs 72.7%, $P = 0.631$ for colon cancer) but a significantly higher proportion of deaths within 25 months (55.2% vs 35.2%, $P = 0.028$ for rectal cancer; 74.1% vs 50.0%, $P = 0.014$ for colon cancer). Among those survived longer than 25 months, young patients had a more favorable long-term survival (log-rank $P = 0.014$ and log-rank $P = 0.040$ for rectal and colon cancers, respectively).

Our second aim was to define whether chemotherapy regimens are associated with different outcomes between young and old patients. Compared with older patients, young patients with CRC were more likely to receive postoperative chemotherapy in each stage, especially multiagent chemotherapy. However, treatment with or without chemotherapy did not significantly improve survival for young patients in each stage, while old patients benefited greatly in high-risk stage II and stage III. Moreover, older patients with high-risk stage II and stage III disease showed more favorable survival with oxaliplatin-based doublet chemotherapy (FOLFOX or

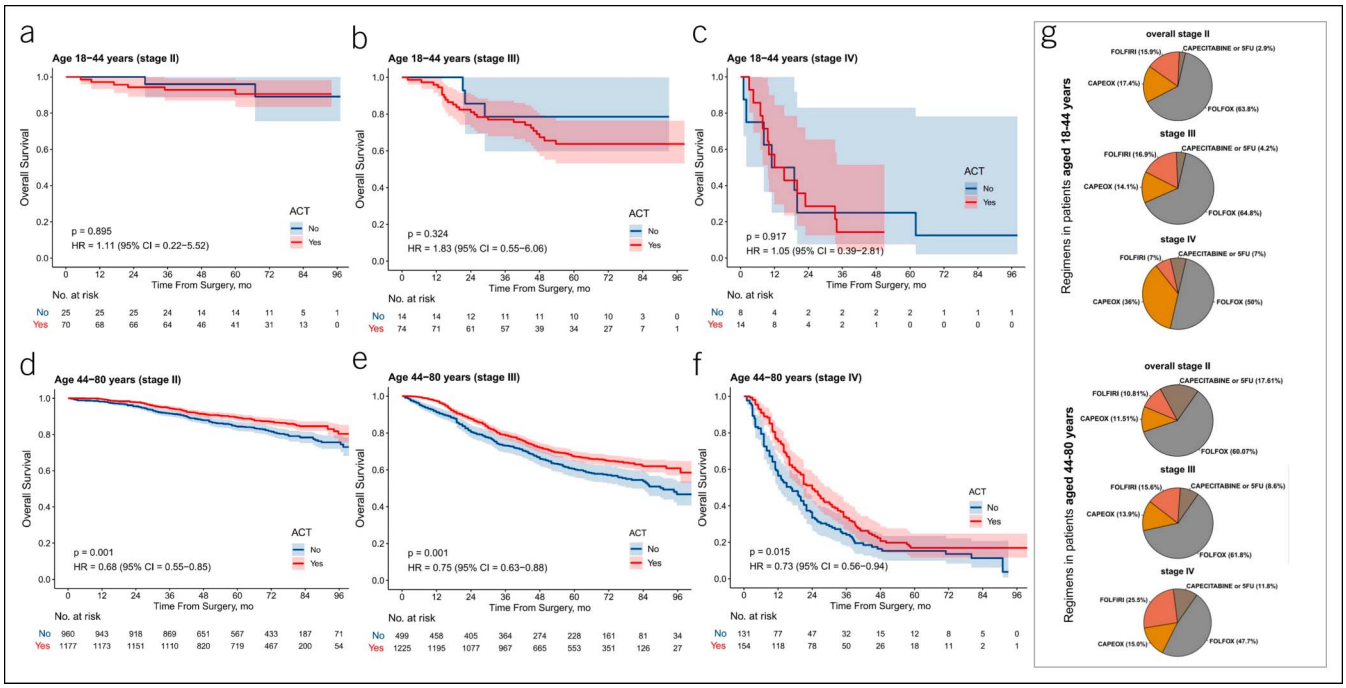

Figure 2. Kaplan-Meier estimates of overall survival stratified by the use of postoperative chemotherapy. Young patients aged 18–44 years with stage II (**a**), stage III (**b**), and stage IV CRC (**c**). Older patients aged 44–80 years with stage II (**d**), stage III (**e**), and stage IV CRC (**f**). (**g**) Chemotherapy regimens in young and old patients with stage II and III CRC. CRC, colorectal cancer.

CAPEOX), which was not observed in young patients. This poor response to oncological treatment could partly account for the increased early mortality observed in young patients. Thus, determining whether the treatment of young patients is appropriate according to the current guidelines should be emphasized. Meanwhile, unraveling the causative mechanisms of young-onset CRC requires further identification to guide personalized treatment.

In our population, young patients were more likely to display adverse histopathological features, including poor differentiation, venous invasion, and MMR deficiency, further corroborating previous findings (18,36,37). Previous studies revealed that young-onset CRC tended to be more advanced at initial diagnosis (11,17,18,36), but this difference was not statistically significant in this study, which may be due to our high selection of patients with stage IV disease to include only those who underwent surgical resection. Although young patients are often not clinically suspected of having CRC, it has been suggested that the advanced stage at diagnosis cannot be explained simply by a longer time to diagnosis in young patients with CRC (38).

CRC with MMR deficiency, characterized by microsatellite instability, has special clinical and pathologic features, such as undifferentiated histology, mucin production, preferential proximal location, and more tumor-infiltrating lymphocytes (36,39–41). In our population, a much higher proportion of young patients with CRC exhibited deficient mismatch repair (dMMR) (33.1%) relative to old patients (17.9%), which was comparable with other reports from Asia (18,42) and Western countries (19,43,44). This high proportion of dMMR can partly account for the adverse histopathological features of young-onset CRC. Moreover, patients with stage II disease more frequently had dMMR and showed a significantly better OS (see Supplementary Figure S1b, Supplementary Digital Content 1, http://links.lww.com/CTG/A888), which could be explained by previous findings that patients with stage II dMMR CRC had an excellent prognosis (41). An age-related bimodal distribution in the proportion of dMMR tumors has been reported, with peaks in patients younger than 45years and older than 70 years and an even higher peak observed among patients older than 80 years (45,46). The expression of *MMR* was different with age, with the loss of expression of *MLH1* in older patients most likely due to sporadic tumors with *MLH1* hypermethylation or *BRAF V600E* mutations while the loss of expression of *MSH2* in younger patients more likely to represent LS. However, LS could only account for a small proportion of dMMR tumors. In a screening for LS in Chinese population, 2.9% of patients with CRC with dMMR detected were diagnosed with LS (47). According to a meta-analysis including 51 studies, the prevalence of LS in patients with dMMR tumors is only 1.6% (48). The high proportion of dMMR in young-onset CRC was irrespective of family history (18,44). Because not all patients with dMMR detected underwent further genetic testing, additional analysis after exclusion of dMMR tumors was performed to further reduce potential bias, and we found the trend was consistent with our findings (see Supplementary Figure S7, Supplementary Digital Content 1, http://links.lww.com/CTG/A888). The underlying mechanisms of the different outcomes and drug responses between young and old patients remain to be discovered.

There are potential limitations to our study. First, the relatively small sample size of young patients with CRC limited our ability to evaluate the association between specific chemotherapy therapies and survival. Second, not all patients underwent genetic testing for inherited syndromes; therefore, some patients, such as those with LS, might have been missed. Third, some important molecular prognostic biomarkers, such as *p53*, *KRAS*, and *BRAF* mutations, were not measured in our study; thus, their association with the etiology and prognosis of young-onset CRC was not explored. Fourth, as discussed earlier, for patients with stage IV

CRC, we included only those who underwent surgical resection; thus, the associated conclusions should be interpreted cautiously. In addition, because we do not have individual data about some risk factors such as obesity, smoking, alcohol consumption, and diabetes mellitus, which have been suggested to be associated with early-onset CRC (49–51), we were not able to consider this aspect in the multivariate analysis, and the results of the adjusted analyses need to be interpreted with some caution.

To the best of our knowledge, this is the first study to demonstrate the survival of young-onset CRC with landmark analysis. We found it unique that young patients with CRC would experience an increased early mortality in the first 25 months after operation but would have superior long-term survival outcomes if they survived for more than 25 months. Second, we confirmed that young patients tended to be overtreated, even those with stage I or low-risk stage II disease, but unlike older patients, they exhibited a very poor response to chemotherapy across all stages, and their survival did not significantly differ based on the treatment regimen administered. Then, we corroborated the adverse histopathological features of young-onset CRC. Above all, the overuse of chemotherapy led to no meaningful survival improvement among young patients, which suggests that clinical practice guidelines specific for young-onset CRC may need to be considered.

CONFLICTS OF INTEREST

Guarantor of the article: Chunze Zhang, PhD.

Specific author contributions: C.Z., S.W., Z.Y., K.N. and Y.Z.: conceptualization. X.Z., Z.Z. and Y.L.: methodology. B.Y., S.L., X.Y., X.Z., Y.W., R.X., W.W., H.L., Y.Z., H.M., X.Z. and H.P.: data collection. Y.H., W.G., X.J. G.W., Z.Z., G.L. and Q.Z.: data analysis. C.Z., S.W., Z.Y. and K.N.: writing—original draft preparation. C.Z., S.W., Z.Y., K.N., Y.Z., Y.H., W.G., X.J. and Q.Z.: writing—review and editing. S.W. and Z.Y.: supervision. All authors have read and agreed to the published version of the manuscript.

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Study Highlights

WHAT IS KNOWN

- ✓ The incidence of young-onset colorectal cancer (CRC) is increasing.
- ✓ The prognosis of young-onset CRC remains controversial.

WHAT IS NEW HERE

- ✓ Young CRC patients experience an increased early mortality but had significantly better long-term survival.
- ✓ Young patients seem to receive more aggressive oncologic therapies, without improvement in clinical outcomes.
- ✓ Young patients have more adverse histopathological features than older patients.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209–49.
2. Vuik FE, Nieuwenburg SA, Bardou M, et al. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. Gut 2019;68(10):1820–6.
3. Siegel RL, Torre LA, Soerjomataram I, et al. Global patterns and trends in colorectal cancer incidence in young adults. Gut 2019;68(12):2179–85.
4. Troeung L, Sodhi-Berry N, Martini A, et al. Increasing incidence of colorectal cancer in adolescents and young adults aged 15-39 years in Western Australia 1982–2007: Examination of colonoscopy history. Front Public Health 2017;5:179.
5. Wong MCS, Huang J, Lok V, et al. Differences in incidence and mortality trends of colorectal cancer worldwide based on sex, age, and anatomic location. Clin Gastroenterol Hepatol 2021;19(5):955–66.e1.
6. Davidson KW, Barry MJ, Mangione CM, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA 2021;325(19):1965–77.
7. O'Connell JB, Maggard MA, Livingston EH, et al. Colorectal cancer in the young. Am J Surg 2004;187(3):343–8.
8. Kanth P, Inadomi JM. Screening and prevention of colorectal cancer. BMJ 2021;374:n1855.
9. Bleyer A, Barr R, Hayes-Lattin B, et al. The distinctive biology of cancer in adolescents and young adults. Nat Rev Cancer 2008;8(4):288–98.
10. Connell LC, Mota JM, Braghiroli MI, et al. The rising incidence of younger patients with colorectal cancer: Questions about screening, biology, and treatment. Curr Treat Options Oncol 2017;18(4):23.
11. Georgiou A, Khakoo S, Edwards P, et al. Outcomes of patients with early onset colorectal cancer treated in a UK specialist cancer center. Cancers (Basel) 2019;11(10):1558.
12. Smith C, Butler JA. Colorectal cancer in patients younger than 40 years of age. Dis Colon Rectum 1989;32(10):843–6.
13. Marble K, Banerjee S, Greenwald L. Colorectal carcinoma in young patients. J Surg Oncol 1992;51(3):179–82.
14. Ezzo JA, Sullivan JF, Mack RE. Carcinoma of the colon under the age of 40. Ann Intern Med 1958;49(2):321–5.
15. Cheng E, Blackburn HN, Ng K, et al. Analysis of survival among adults with early-onset colorectal cancer in the National Cancer Database. JAMA Netw Open 2021;4(6):e2112539.
16. Fu JF, Huang YQ, Yang J, et al. Clinical characteristics and prognosis of young patients with colorectal cancer in Eastern China. World J Gastroenterol 2013;19(44):8078–84.
17. Kneuertz PJ, Chang GJ, Hu CY, et al. Overtreatment of young adults with colon cancer: More intense treatments with unmatched survival gains. JAMA Surg 2015;150(5):402–9.
18. Liang JT, Huang KC, Cheng AL, et al. Clinicopathological and molecular biological features of colorectal cancer in patients less than 40 years of age. Br J Surg 2003;90(2):205–14.
19. Chang DT, Pai RK, Rybicki LA, et al. Clinicopathologic and molecular features of sporadic early-onset colorectal adenocarcinoma: An adenocarcinoma with frequent signet ring cell differentiation, rectal and sigmoid involvement, and adverse morphologic features. Mod Pathol 2012;25(8):1128–39.
20. O'Connell JB, Maggard MA, Liu JH, et al. Do young colon cancer patients have worse outcomes? World J Surg 2004;28(6):558–62.
21. Beckman EN, Gathright JB, Ray JE. A potentially brighter prognosis for colon carcinoma in the third and fourth decades. Cancer 1984;54(7): 1478–81.
22. Yang Z, Kang L, Wang L, et al. Characteristics and long-term survival of colorectal cancer patients aged 44 years and younger. Clin Transl Oncol 2012;14(12):896–904.
23. Weinberg BA, Marshall JL, Salem ME. The growing challenge of young adults with colorectal cancer. Oncology (Williston Park) 2017;31(5): 381–9.
24. Hendifar A, Yang D, Lenz F, et al. Gender disparities in metastatic colorectal cancer survival. Clin Cancer Res 2009;15(20):6391–7.
25. Rosato V, Bosetti C, Levi F, et al. Risk factors for young-onset colorectal cancer. Cancer Causes Control 2013;24(2):335–41.
26. Chinese Society of Clinical Oncology CSCO Diagnosis and Treatment Guidelines for Colorectal Cancer Working Group. Chinese Society of Clinical Oncology (CSCO) diagnosis and treatment guidelines for colorectal cancer 2018 (English version). Chin J Cancer Res 2019;31(1): 117–34.

27. Abd ElHafeez S, D'Arrigo G, Leonardis D, et al. Methods to analyze time-to-event data: The cox regression analysis. Oxid Med Cell Longev 2021; 2021:1302811.
28. Sung JJY, Chiu HM, Jung KW, et al. Increasing trend in young-onset colorectal cancer in Asia: More cancers in men and more rectal cancers. Am J Gastroenterol 2019;114(2):322–9.
29. Deng Y. Rectal cancer in Asian vs. western countries: Why the variation in incidence? Curr Treat Options Oncol 2017;18(10):64.
30. Chan KK, Dassanayake B, Deen R, et al. Young patients with colorectal cancer have poor survival in the first twenty months after operation and predictable survival in the medium and long-term: Analysis of survival and prognostic markers. World J Surg Oncol 2010;8(1):82.
31. Zhao L, Zhang W, Ma D, et al. Analysis of colorectal cancer screening practices in the general population of Tianjin. Chin J Clin Oncol 2015; 42(15):760–4.
32. Huang Q, Tian C. Visualizing time-varying effect in survival analysis: 5 complementary plots to Kaplan-Meier curve. Oxid Med Cell Longev 2022;2022:3934901.
33. Manjelievskaia J, Brown D, McGlynn KA, et al. Chemotherapy use and survival among young and middle-aged patients with colon cancer. JAMA Surg 2017;152(5):452–9.
34. Saraste D, Järås J, Martling A. Population-based analysis of outcomes with early-age colorectal cancer. Br J Surg 2020;107(3):301–9.
35. Perera T, Wijesuriya RE, Suraweera PH, et al. The prevalence of colorectal cancer and survival in patients from the Gampaha District, North Colombo region. Ceylon Med J 2008;53(1):17–21.
36. Zaborowski AM, Abdile A, Adamina M, et al. Characteristics of early-onset vs late-onset colorectal cancer: A review. JAMA Surg 2021;156(9): 865–74.
37. Álvaro E, Cano JM, García JL, et al. Clinical and molecular comparative study of colorectal cancer based on age-of-onset and tumor location: Two main criteria for subclassifying colorectal cancer. Int J Mol Sci 2019; 20(4):968.
38. Chen FW, Sundaram V, Chew TA, et al. Advanced-stage colorectal cancer in persons younger than 50 years not associated with longer duration of symptoms or time to diagnosis. Clin Gastroenterol Hepatol 2017;15(5): 728–37.e3.
39. Ahnen DJ, Wade SW, Jones WF, et al. The increasing incidence of young-onset colorectal cancer: A call to action. Mayo Clin Proc 2014;89(2): 216–24.
40. Calin GA, Gafà R, Tibiletti MG, et al. Genetic progression in microsatellite instability high (MSI-H) colon cancers correlates with clinico-pathological parameters: A study of theTGRβRII, BAX, hMSH3, hMSH6, IGFIIR andBLM genes. Int J Cancer 2000;89(3): 230–5.
41. Kawakami H, Zaanan A, Sinicrope FA. Microsatellite instability testing and its role in the management of colorectal cancer. Curr Treat Options Oncol 2015;16(7):30.
42. Chan TL, Yuen ST, Chung LP, et al. Frequent microsatellite instability and mismatch repair gene mutations in young Chinese patients with colorectal cancer. J Natl Cancer Inst 1999;91(14):1221–6.
43. Farrington SM, Lin-Goerke J, Ling J, et al. Systematic analysis of hMSH2 and hMLH1 in young colon cancer patients and controls. Am J Hum Genet 1998;63(3):749–59.
44. Liu B, Farrington SM, Petersen GM, et al. Genetic instability occurs in the majority of young patients with colorectal cancer. Nat Med 1995;1(4): 348–52.
45. Chao A, Gilliland F, Willman C, et al. Patient and tumor characteristics of colon cancers with microsatellite instability: A population-based study. Cancer Epidemiol Biomarkers Prev 2000;9(6):539–44.
46. Yiu R, Qiu H, Lee SH, et al. Mechanisms of microsatellite instability in colorectal cancer patients in different age groups. Dis Colon Rectum 2005; 48(11):2061–9.
47. Jiang W, Cai MY, Li SY, et al. Universal screening for Lynch syndrome in a large consecutive cohort of Chinese colorectal cancer patients: High prevalence and unique molecular features. Int J Cancer 2019;144(9): 2161–8.
48. Abu-Ghazaleh N, Kaushik V, Gorelik A, et al. Worldwide prevalence of Lynch syndrome in patients with colorectal cancer: Systematic review and meta-analysis. Genet Med 2022;24(5):971–85.
49. Kim NH, Jung YS, Yang HJ, et al. Prevalence of and risk factors for colorectal neoplasia in asymptomatic young adults (20-39 years old). Clin Gastroenterol Hepatol 2019;17(1):115–22.
50. Liu PH, Wu K, Ng K, et al. Association of obesity with risk of early-onset colorectal cancer among women. JAMA Oncol 2019;5(1):37–44.
51. Islami F, Goding Sauer A, Miller KD, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin 2018;68(1):31–54.