Original Research Article

Cancer Control
Volume 29: 1–9
© The Author(s) 2022
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/10732748221096842
journals.sagepub.com/home/ccx
SAGE

Clinicogenomic Characteristics and Treatment of Young-Onset Colorectal Cancer Patients Treated With Palliative Therapy in Real-World Practice

Hyehyun Jeong[1], Eunjung Lee[2], Deokhoon Kim[2,3], Jihun Kim[3], Sun Young Kim[1], Yong Sang Hong[1], Tae Won Kim[1,†], and Jeong Eun Kim[1,†]

Abstract

Introduction: Young-onset colorectal cancer (YOCR) is increasing. This study aimed to determine the difference between advanced YOCR and non-YOCR patient outcomes.

Methods: We retrospectively included patients with recurrent/metastatic colorectal cancer treated with palliative systemic therapy between 2016 and 2018. Diagnosis at < 50 years was defined as YOCR. Targeted sequencing was used to assess the mutational status.

Results: Among the 969 patients included, 210 (21.7%) were YOCR. The median progression-free survival with first-line chemotherapy (PFS1) was 9.7 vs 9.4 months ($P = .755$), and the median overall survival (OS) was 25.9 vs 22.3 months ($P = .581$) in the YOCR and the non-YOCR group, respectively. However, the youngest patients diagnosed at < 30 years showed poorer survival outcomes (median PFS1, 3.9 months; median OS, 8.6 months) compared with other age groups. PFS1 did not differ between YOCR and non-YOCR by choice of treatment regimen. Among the 340 patients with targeted sequencing results, YOCR had fewer *APC* mutations (61% vs 80%), but had similar *KRAS* (53% vs 48%), *NRAS* (7% vs 3%), and *BRAF* class I mutations (4% vs 6%). The median tumor mutational burden (TMB) was 10.9 vs 12.5 mut/Mb in YOCR and non-YOCR patients, respectively ($P = .064$). TMB increased with age in tumors with high microsatellite instability (Pearson's $R = .69$, $P = .028$), but not in microsatellite-stable tumors ($R = .02$, $P = .658$).

Conclusions: Survival outcomes with palliative systemic therapy were similar between recurrent/metastatic YOCR and non-YOCR with an age cut-off of 50 years. However, patients diagnosed at < 30 years of age showed poorer outcomes compared with other age groups.

[1]Department of Oncology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea
[2]Department of Medical Science, University of Ulsan College of Medicine, Asan Medical Institute of Convergence Science and Technology, Asan Medical Center, Seoul, Republic of Korea
[3]Department of Pathology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea

[†]Tae Won Kim and Jeong Eun Kim contributed equally as co-corresponding authors.

Corresponding Authors:
Tae Won Kim, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Seoul, Republic of Korea.
Email: twkimmd@amc.seoul.kr

Jeong Eun Kim, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Seoul, Republic of Korea.
Email: jeongeunkim@amc.seoul.kr

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

Keywords
colorectal cancer, young-onset colorectal cancer, palliative chemotherapy, targeted sequencing, tumor mutational burden

Introduction

Although the median age of diagnosis of colorectal cancer is approximately in the mid-sixties and more than 88% of new colorectal cases in the USA are > 50 years old at the time of diagnosis,[1] recent trends in the incidence of colorectal cancer are noticeably different between age groups. Between 2011 and 2016, colorectal cancer incidence decreased by 3.3%/year in patients aged ≥ 65 years, whereas it increased by 2.2%/year in patients aged < 50 years, and the increase in the incidence was more prominent in patients aged < 40 years.[2,3] These alarming trends in the increase of young-onset colorectal cancer (YOCR) are observed across continents, including East Asia, Europe, and Australia,[4,5] and expected to continue to rise in the next 2 decades.[6]

However, the difference in the clinicogenomic features and outcomes of YOCR and non-YOCR patients is yet to be determined. Previous studies suggested some features that may differentiate YOCR from non-YOCR, including advanced stage at presentation, left-sidedness, or poor differentiation.[7,8] The reasons for these differences are not fully understood. As for the survival outcomes for YOCR, previous studies used heterogeneous age definitions for YOCR, often included heterogeneous patients with different disease stages, and produced contradictory results on the survival outcomes.[9-11] Moreover, the effectiveness of specific chemotherapy regimens for YOCR patients was rarely described. Considering that YOCR patients constitute only 13%–15% of colorectal cancer clinical trial participants,[12,13] the results of many clinical trials in colorectal cancer might not sufficiently reflect the outcome of YOCR patients. Therefore, further research is needed to determine if age-tailored treatment strategies are necessary in advanced-stage YOCR patients.

This study aimed to identify distinct clinical and genomic features of the YOCR patients and to analyze the impact of age and treatment regimen on the outcomes of YOCR patients, specifically patients with recurrent/metastatic disease treated with palliative systemic therapy.

Methods

Patients

Patients with recurrent or metastatic colorectal cancer patients who were treated with palliative systemic therapy between January 2016 and December 2018 in the Asan Medical Center, a tertiary referral center in Seoul, Republic of Korea, were retrospectively identified and included in this study. All individual patient data were de-identified. This study was approved by the Institutional Review Board (IRB) of the Asan Medical Center and conducted in accordance with the principles of the Declaration of Helsinki. The IRB waived the requirement for informed consent for this retrospective study.

Assessments, Bioinformatics Analysis, and Statistical Analysis

In this study, colorectal cancer diagnosed at < 50 years of age was defined as YOCR and the others were defined as non-YOCR. Progression-free survival (PFS) was defined as the time from the start of palliative systemic therapy to the time of disease progression or death of any cause, whichever occurred first. PFS1 and PFS2 indicate PFS with the palliative first-line and second-line treatment, respectively. Overall survival (OS) was defined as the time from the start of first-line palliative chemotherapy to the time of death of any cause. For targeted exome sequencing, an in-house panel of the Asan Medical Center (OncoPanel AMC, versions 3 and 4[14,15]) was used from previously collected, formalin-fixed, paraffin-embedded tissue specimens.

Baseline characteristics were analyzed and compared using descriptive methods. Survival outcomes were estimated using the Kaplan–Meier method and compared using a log-rank test. The association between age at diagnosis and survival outcomes was assessed using the Cox proportional hazards model and restricted cubic splines curves with age treated as a continuous variable. The correlation between the age of diagnosis and the tumor mutational burden (TMB) was assessed using the Pearson's R correlation coefficient. All tests were two-sided, and P values < .05 were considered statistically significant. Statistical analyses were performed using R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria). The reporting of this study conforms to STROBE guidelines.[16]

Results

Patients

A total of 990 recurrent or metastatic colorectal cancer who received palliative systemic therapy during the study period were identified. Among those, 21 patients were excluded because the dates of first chemotherapy were not available, leaving a total of 969 patients for analysis. Among those, 210 (21.7%) were diagnosed at age < 50 years (YOCR group), while the remaining 759 (78.3%) were diagnosed at age ≥ 50 years (non-YOCR group). The baseline characteristics of the patients by age of onset are listed in Table 1. Overall, these baseline characteristics, including sex, sidedness, tumor grade,

Table 1. Baseline Characteristics.

	YOCR N = 210	Non-YOCR N = 759	*P* Value
Age at diagnosis			
Median (range)	44 (25-49)	62 (50-88)	<.001
Sex			
Male	111 (52.9)	478 (63.0)	.008
Female	99 (47.1)	281 (37.0)	
Primary tumor location			
Right	37 (17.6)	204 (26.9)	.036
Left	93 (44.3)	317 (41.8)	
Rectum	80 (38.1)	235 (31.0)	
Multiple	0 (.0)	2 (.3)	
Unknown	0 (.0)	1 (.1)	
Tumor grade			
Well differentiated	11 (5.2)	71 (9.4)	.074
Moderately differentiated	154 (73.3)	564 (74.3)	
Poorly differentiated	30 (14.3)	72 (9.5)	
Unknown	15 (7.1)	52 (6.9)	
Histology			
Adenocarcinoma	194 (92.4)	707 (93.1)	.890
Signet ring cell	2 (1.0)	9 (1.2)	
Others	14 (6.7)	43 (5.7)	
Stage at diagnosis			
I-II	11 (5.2)	62 (8.2)	.273
III	46 (21.9)	144 (19.0)	
IV	153 (72.9)	553 (72.9)	
MSI status by PCR	N = 106	N = 379	.239
MSS/MSI-L	99 (93.4)	366 (96.6)	
MSI-H	7 (6.6)	13 (3.4)	
MMR by IHC	N = 155	N = 507	>.99
pMMR	147 (94.8)	482 (95.4)	
dMMR	8 (5.2)	25 (4.9)	
RAS by PCR	N = 206	N = 705	.692
Wild	95 (46.1)	337 (47.8)	
Mutant	111 (53.9)	368 (52.2)	
BRAF by PCR	N = 198	N = 694	.988
Wild	187 (94.4)	653 (94.1)	
Mutant	11 (5.6)	41 (5.9)	
Lines of treatment given			
1	49 (23.3)	185 (24.4)	.066
2	73 (34.8)	319 (42.0)	
3 and above	88 (41.9)	255 (33.6)	
Palliative 1st line regimen			
FOLFOX/FOLFIRI + bevacizumab	149 (71.0)	531 (70.0)	.847
FOLFOX/FOLFIRI + cetuximab	41 (19.5)	134 (17.7)	.602
FOLFOX/FOLFIRI	17 (8.1)	73 (9.6)	.590
Others	3 (1.4)	21 (2.8)	.393
Palliative 2nd line regimen	N = 161	N = 574	
FOLFOX/FOLFIRI + bevacizumab	123 (76.4)	456 (79.4)	.468
FOLFOX/FOLFIRI/irinotecan + cetuximab	2 (1.2)	6 (1.0)	.689
FOLFOX/FOLFIRI	17 (10.6)	58 (10.1)	.983
Others	19 (11.8)	54 (9.4)	.454

Note: Data are shown as number (%) unless indicated otherwise.

Abbreviations: dMMR, deficient mismatch repair; FOLFOX, 5-fluorouracil + oxaliplatin; FOLFIRI, 5-fluorouracil + irinotecan; MSI-H, high microsatellite instability; MSI-L, low microsatellite instability; MSS, microsatellite-stable; pMMR, proficient mismatch repair.

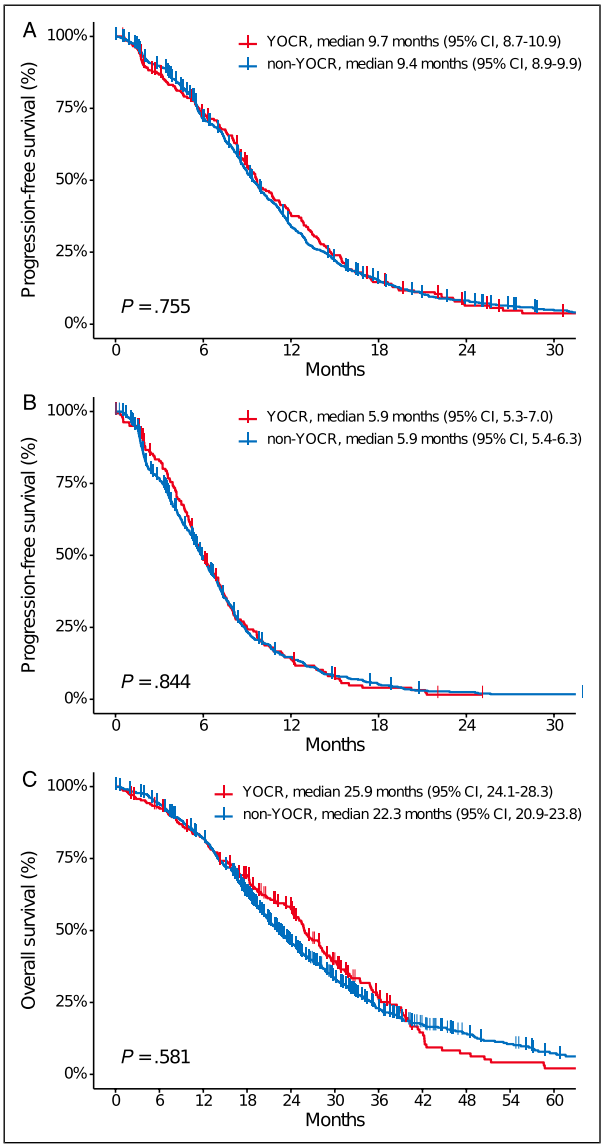

Figure 1. Survival outcomes in the entire study population. (A) Progression-free survival (PFS) with first-line treatment, (B) PFS with second-line treatment, and (C) overall survival. Abbreviations: CI, confidence interval; YOCR, young-onset colorectal cancer.

histology, and stage at diagnosis were not significantly different between groups. Polymerase chain reaction-based microsatellite instability (MSI) status was available in 485 patients; among those, 7 out of 106 patients (6.6%) in the YOCR group and 13 out of 379 patients (3.4%) in the non-YOCR group had high microsatellite instability (MSI-H) tumors (P = .239).

Treatment patterns were similar between groups. All patients received chemotherapy with palliative intent, with 190 patients (90.4%) in the YOCR group and 665 patients (87.6%) in the non-YOCR group treated with FOLFOX (5-fluorouracil/oxaliplatin) or FOLFIRI (5-fluorouracil/irinotecan) regimen with targeted agents as first-line treatment. As for targeted agents in the first-line treatment, bevacizumab was administered to 151 patients (71.9%) in the YOCR group and 534 patients (70.4%) in the non-YOCR group. Cetuximab was administered to 41 (19.5%) patients in the YOCR group and 136 patients (17.9%) in the non-YOCR group.

The number of patients who achieved complete surgical resection after initially-palliative-intent chemotherapy was 4 (1.9%) in the YOCR group and 9 (1.2%) in the non-YOCR group.

Survival Outcomes

The median follow-up duration was 41.9 months (95% confidence interval [CI], 39.1-44.6). During follow-up, median lines of chemotherapy given were 2 (range: 1-6) in the YOCR group and 2 (range: 1-7) in the non-YOCR group. Median PFS with first-line chemotherapy (PFS1) was 9.7 months (95% CI, 8.7-10.9) in the YOCR group vs 9.4 months (95% CI, 8.9-9.9) in the non-YOCR group (P = .755) (Figure 1A). Median PFS with second-line chemotherapy (PFS2) was 5.9 months (95% CI, 5.3-7.0) in the YOCR group vs 5.9 months (95% CI, 5.4-6.3) in the non-YOCR group (P = .844) (Figure 1B). Median OS was 25.9 months (95% CI, 24.1-28.3) in the YOCR group vs 22.3 months (95% CI, 20.9-23.8) in the non-YOCR group (P = .581) (Figure 1C). Progression-free survival with first-line chemotherapy and OS also did not differ between YOCR and non-YOCR patients in all subgroups stratified by *RAS* or *BRAF* mutation status (Supplementary Figure S1).

Survival Outcomes by Treatment

We compared PFS1 of YOCR and non-YOCR groups according to the first-line treatment regimen and MSI status. In left-sided tumors including rectal cancers, the median PFS1 with bevacizumab-chemotherapy combinations was 10.5 months (95% CI, 9.3-12.0) in the YOCR group (N = 119) vs 9.5 months (95% CI, 8.8-10.0) in the non-YOCR group (N = 375) (P = .131). In cetuximab-chemotherapy combination-treated left-sided tumors, the median PFS1 was 13.4 months (95% CI, 8.4-15.4) in the YOCR group (N = 37) vs 12.0 months (95% CI, 10.8-13.0) (N = 117) in the non-YOCR group (P = .714) (Figure 2A). In right-sided tumors, the median PFS1 with bevacizumab-chemotherapy combinations was 8.4 months (95% CI, 5.8-9.6) in the YOCR group (N = 32) vs 8.8 months (95% CI, 8.0-9.8) in the non-YOCR group (N = 156) (P = .368). The median PFS1 with cetuximab-chemotherapy combinations was 4.6 months (95% CI, 1.6–not estimated [NE]) in the YOCR group (N = 4) vs 10.7 months (95% CI, 7.3-13.2) in the non-YOCR group (N = 19) (P = .069) (Figure 2B).

Progression-free survival with first-line chemotherapy did not significantly differ between the YOCR and non-YOCR groups in

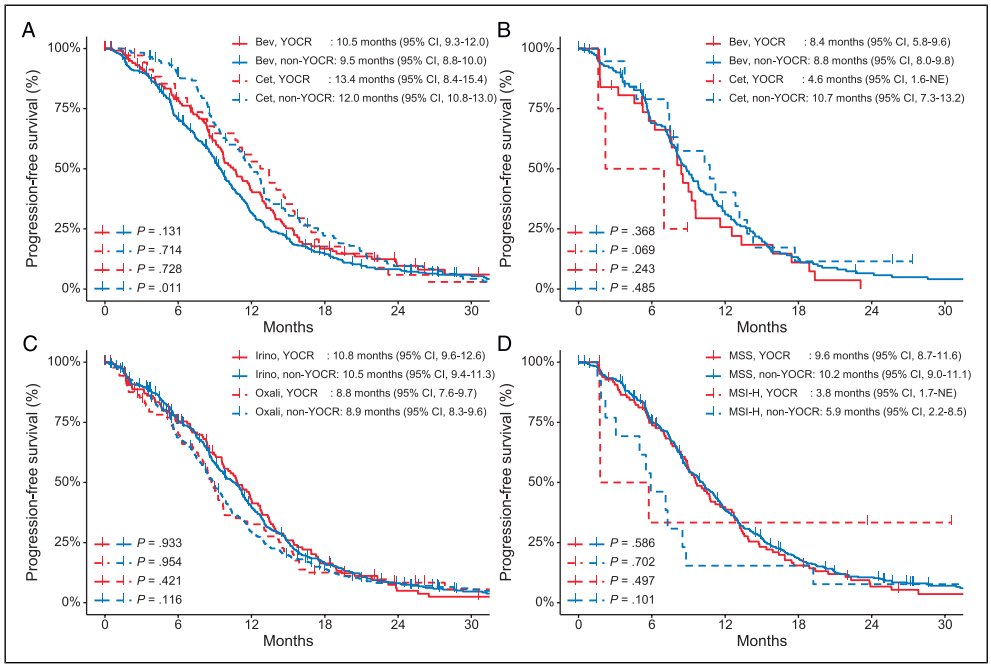

Figure 2. Progression-free survival with first-line treatment by regimen. (A) With bevacizumab- or cetuximab-containing regimens in left sided tumor and (B) in right sided tumor, (C) with irinotecan- or oxaliplatin-based regimens, and (D) by microsatellite instability status. AbbreviationsBev, bevacizumab; Cet, cetuximab; CI, confidence interval; YOCR, young-onset colorectal cancer, Irino, irinotecan; MSS, microsatellite-stable; MSI-H, high microsatellite instability; Oxali, oxaliplatin. Note: P values refer to log-rank tests and unadjusted for pairwise comparisons.

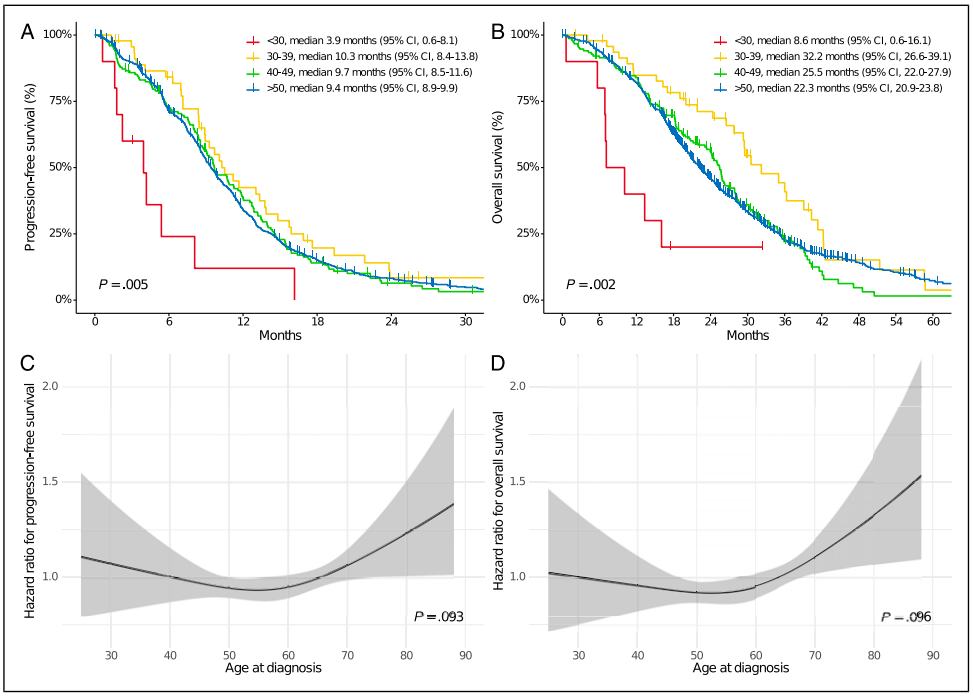

Figure 3. Kaplan-Meier estimate of (A) progression-free survival with first-line treatment (PFS1) and (B) overall survival (OS) in detailed groups by age at diagnosis, and unadjusted hazard ratio for (C) PFS1 and (D) OS by age at diagnosis as a continuous variable. AbbreviationsCI, confidence interval.

Table 2. Summarization of Targeted Gene Sequencing Results.

Genes	Total N = 340	YOCR N = 77	Non-YOCR N = 263	*P* Value
Most commonly mutated genes (top 20)				
TP53	277 (81.5)	62 (80.5)	215 (81.7)	.740
APC	258 (75.9)	47 (61.0)	211 (80.2)	.001
KRAS	168 (49.4)	41 (53.2)	127 (48.3)	.517
PIK3CA	67 (19.7)	16 (20.8)	51 (19.4)	.871
SMAD4	61 (17.9)	12 (15.6)	49 (18.6)	.615
FBXW7	48 (14.1)	8 (10.4)	40 (15.2)	.354
BRCA2	45 (13.2)	10 (13.0)	35 (13.3)	>.99
LRP1B	44 (12.9)	6 (7.8)	38 (14.4)	.175
BRAF	30 (8.8)	4 (5.2)	26 (9.9)	.257
ARID1A	28 (8.2)	4 (5.2)	24 (9.1)	.349
ATM	28 (8.2)	6 (7.8)	22 (8.4)	.99
NF1	26 (7.6)	5 (6.5)	21 (8)	.810
KMT2A	22 (6.5)	2 (2.6)	20 (7.6)	.185
NOTCH4	22 (6.5)	7 (9.1)	15 (5.7)	.297
BRCA1	22 (6.5)	6 (7.8)	16 (6.1)	.602
GNAS	22 (6.5)	6 (7.8)	16 (6.1)	.602
RNF43	21 (6.2)	6 (7.8)	15 (5.7)	.590
NOTCH1	21 (6.2)	5 (6.5)	16 (6.1)	>.99
ASXL1	20 (5.9)	5 (6.5)	15 (5.7)	.786
POLE	20 (5.9)	5 (6.5)	15 (5.7)	.786
Differentially mutated genes				
APC	258 (75.9)	47 (61.0)	211 (80.2)	.001
ROS1	19 (5.6)	8 (10.4)	11 (4.2)	.049
Other genes of interest				
NRAS	14 (4.1)	5 (6.5)	9 (3.4)	.324
BRAF				
Class I	18 (5.3)	3 (3.9)	15 (5.7)	.773
Others	12 (3.5)	1 (1.3)	11 (4.2)	.311
HER2 amplification	12 (3.5)	4 (5.2)	8 (3.0)	.480
Pathway mutations				
TP53	290 (85.3)	65 (84.4)	225 (85.6)	.949
RTK-RAS	276 (81.2)	61 (79.2)	215 (81.7)	.739
Wnt	273 (80.3)	52 (67.5)	221 (84.0)	.002
PI3K	135 (39.7)	32 (41.6)	103 (39.2)	.806
NOTCH	110 (32.4)	21 (27.3)	89 (33.8)	.345
TGF-beta	80 (23.5)	19 (24.7)	61 (23.2)	.907
Cell cycle	31 (9.1)	11 (14.3)	20 (7.6)	.117
Hippo	9 (2.6)	3 (3.9)	6 (2.3)	.429
MYC	8 (2.4)	2 (2.6)	6 (2.3)	>.99

Abbreviation: YOCR, young-onset colorectal cancer.

patients treated with first-line oxaliplatin- or irinotecan-based regimens (in oxaliplatin-treated patients, median 8.8 months [95% CI, 7.6-9.7] in the YOCR group [N = 92] vs 8.9 months [95% CI, 8.3-9.6] in the non-YOCR group [N = 369], P = .954; in irinotecan-treated patients, median 10.8 months [95% CI, 9.6-12.6] in the YOCR group [N = 118] vs 10.5 months [95% CI, 9.4-11.3] in the non-YOCR group [N = 372], P = .933) (Figure 2C).

Among patients with microsatellite-stable (MSS) disease confirmed by polymerase chain reaction-based analysis, the median PFS1 was 9.6 months (95% CI, 8.7-11.6) in the YOCR group (N = 99) vs 10.2 months (95% CI, 9.0-11.1) in the non-YOCR group (N = 366) (*P* = .586). Patients with MSI-H tumors had a median PFS1 of 3.8 months (95% CI, 1.7–NE) in the YOCR group (N = 7) and 5.9 months (95% CI, 2.2-8.5) in the non-YOCR group (N = 13) (*P* = .702).

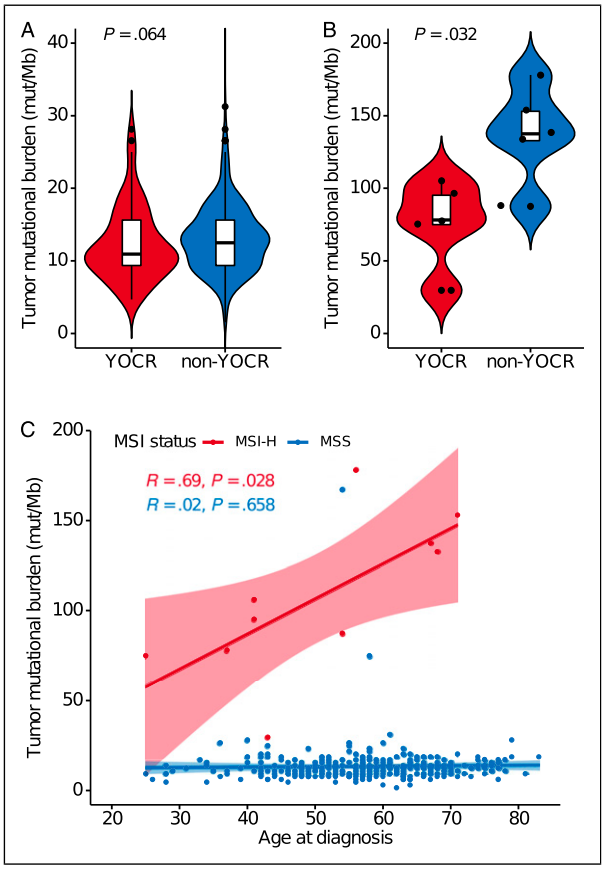

Figure 4. Tumor mutational burden in patients with (A) microsatellite-stable tumors, (B) high microsatellite instability, and (C) Pearson correlation between age and tumor mutational burden. AbbreviationsYOCR, young-onset colorectal cancer; MSI, microsatellite instability.

Survival Outcomes by Detailed Age Group

Additionally, we analyzed survival outcomes according to more detailed age groups where patients diagnosed at age < 50 years were divided by age deciles (< 30 years [N = 10, 1.0%], 30-39 years [N = 48, 5.0%], 40-49 [N = 152, 15.7%], and ≥ 50 years [N = 759, 78.3%]). Patients who were diagnosed at < 30 years of age showed a shorter PFS1 and OS (median PFS, 3.9 months [95% CI, .6-8.1]; median OS, 8.6 months [95% CI, .6-16.1]) compared with other age groups (Figure 3A–B).

In a univariable Cox regression analysis for PFS1 and OS according to age as a continuous variable, age showed a borderline statistical significance for nonlinear association (*P*

= .093 for PFS1, P = .096 for OS), with hazard ratios increasing at the extremes of age (Figure 3C–D).

Genomic Analysis by Targeted Sequencing

A total of 340 patients had available targeted sequencing results from tumor tissues. The results of targeted sequencing were compared between patients diagnosed < 50 years (YOCR; N = 77, 22.6%) and those ≥ 50 years (non-YOCR; N = 263, 77.4%). Overall, the most commonly mutated genes were *TP53, APC, KRAS, PIK3CA*, and *SMAD4* in both YOCR and non-YOCR patients (Table 2). Fewer patients had *APC* mutation in the YOCR group (61.0% [n = 47/77] of YOCR vs 80.2% [N = 211/263] of non-YOCR, P = .001), whereas *ROS1* mutation (10.4% [N = 8/77] of YOCR vs 4.2% [N = 11/263] of non-YOCR, P = .049) was more frequent in the YOCR group. Wnt pathway mutation was less frequent in the YOCR group (67.5% [N = 52/77] in the YOCR vs 84.0% [N = 221/263] in the non-YOCR group, P = .002).

Tumor Mutational Burden

Tumor mutational burden was calculated from targeted gene sequencing results[14] in the aforementioned 340 patients. Among those, 10 patients (2.9%) were MSI-H, and 330 patients (97.1%) were MSS by targeted sequencing. In MSS tumors, the median TMB was 10.9 mut/Mb [range, 4.7-28.1] vs 12.5 mut/Mb [range, 1.6-167.2] in YOCR (N = 72) and non-YOCR (N = 258) patients, respectively (P = .064). In MSI-H tumors, the median TMB was 78.1 mut/Mb [range, 29.7-106.3] and 137.5 mut/Mb [range, 87.5-178.1 in YOCR (N = 5) and non-YOCR (N = 5) patients, respectively (P = .032) (Figure 4A–B). In the MSS group, TMB was not correlated with age at diagnosis (R = .02 by Pearson's correlation, P = .658), whereas in the MSI-H group, TMB increased as the age at diagnosis increased (R = .69, P = .028) (Figure 4C).

Discussion

Currently, the need for age-tailored therapy in patients with advanced colorectal cancer has not been clearly established. Based on a large clinical and genomic dataset on the recurrent/metastatic diseases treated with palliative systemic therapy, this study showed that the survival outcomes of YOCR patients were not inferior to those of non-YOCR patients. However, the youngest subgroup of YOCR patients diagnosed at < 30 years of age demonstrated shorter survival outcomes compared with other age groups. The YOCR group showed several distinct features, including fewer *APC* mutations and Wnt pathway alterations in terms of genomic alterations by targeted sequencing, Also, in patients with MSI-H tumors, TMB increased with age, whereas in MSS patients, it did not.

The treatment regimens used in this study cohort were mostly 5-fluorouracil-based doublet with irinotecan or oxaliplatin combined with targeted agents (> 87% of the patients), and only 1 patient in the non-YOCR group received triplet chemotherapy containing both irinotecan and oxaliplatin. Overall, all the survival outcomes measured including PFS1, PFS2, and OS did not differ between the YOCR and non-YOCR patients. Moreover, we looked into the survival outcomes by treatment regimens and observed no significant differences in PFS1 by the choice of chemotherapy agents or targeted agents in both age groups. Although it has been reported that YOCR patients tend to receive more aggressive treatment including triplet chemotherapy,[17] evidence is lacking on the survival benefit of such approach. Our findings suggest that survival outcomes of YOCR did not differ from those of non-YOCR who underwent similar systemic treatment.

One of the important issues in YOCR is what cutoff value for age should be used for the definition of YOCR. Currently, different definitions of YOCR are used among studies, most commonly around screening ages (40-50 years).[18] We performed additional survival analyses by age deciles among the YOCR patients to determine if prognoses differ in certain age groups before the screening age. As a result, patients diagnosed at < 30 years of age showed significantly poorer survival outcomes compared with other age groups. The poor prognoses of these "very young-onset" colorectal cancers have been suggested in prior studies.[8,19-21] In the univariable Cox proportional hazards model with age treated as a continuous variable, patients of extreme ages showed tendencies toward increased hazard ratios for PFS1 and OS with marginal significance for nonlinear associations, consistent with a previous report.[13] Given that our dataset included only a limited number of patients diagnosed at < 30 years of age, further studies are required to confirm the poor prognoses of very YOCR patients and establish the adequate age cutoff for "young-onset" colorectal cancers.

We observed that YOCR patients had significantly fewer *APC* mutations than non-YOCR patients, which is in line with the results of previous studies.[7,22,23] The lower incidence of the Wnt pathway mutation in the YOCR group is also consistent with the low incidence of the *APC* mutation. However, despite the repeatedly described poor prognosis in *APC* wild-type colorectal cancer,[24,25] the difference in the frequency of *APC* mutation between age groups did not result in different survival outcomes in this study. Overall, both groups showed high frequency of *TP53* mutation (> 84%) which possibly attributed to the advanced disease status of our cohort.[26,27]

Some previous studies reported a higher incidence of MSI-H tumors in YOCR patients.[7] In this study, the proportion of MSI-H tumors was numerically higher in the YOCR group (6.6% vs 3.4% among patients with available results) without statistical significance. Regarding TMB, it did not differ between age groups in MSS tumors (10.9 mut/Mb in the YOCR group vs 12.5 mut/Mb in the non-YOCR group) without significant linear correlations by age. In contrast, the median TMB patients with MSI-H tumors were lower in the YOCR group (78.1 mut/Mb vs 137.5 mut/Mb). Also, the MSI-H

group showed higher TMB with increasing age. In the recent Keynote-177 study, first-line pembrolizumab showed improved PFS in MSI-H/dMMR advanced colorectal cancer.[28] Whether TMB could serve as a predictive marker for treatment response and survival outcomes of MSI-H patients treated with immune checkpoint inhibitors is currently unknown; however, retrospective studies have suggested the relationship between improved response rates and survival outcomes to immune checkpoint inhibitors and high TMB values.[29,30] Taken together with our findings that showed a correlation between age and TMB in MSI-H patients, it is worthy of further investigation if clinical outcomes differ by age in patients treated with immune checkpoint inhibitors for advanced colorectal cancer.

One of the limitations of this study is its single-centered and retrospective nature, and the relatively smaller number of patients in the YOCR group compared with the non-YOCR group, which might attribute the lack of statistical significance in the differences of clinical features between groups. However, the strength of our study lies in the homogeneity of patient population in terms of disease status and treatment as well as the large sample size including targeted sequencing results retrieved from real-world practice. Moreover, our data included detailed information on treatment, which we used for survival outcome analysis by regimens and patient characteristics with long-term follow-up duration. The authors believe that this study provides useful information on the palliative treatment choice of YOCR in daily practice where data on the survival outcomes by specific treatment regimens is limited.

Conclusion

Survival outcomes did not differ between recurrent/metastatic YOCR and non-YOCR patients treated with palliative systemic therapy with an age cut-off of 50 years. However, the outcome of patients aged < 30 years was poorer, with the limitation of a small patient number, and warrants further investigation.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by a grant (2020IP0040) from the Asan Institute for Life Sciences, Asan Medical Center, Seoul, Korea, and by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number : HI18C2383).

Ethics Statement

This study was approved by the Institutional Review Board (IRB) of the Asan Medical Center and conducted in accordance with the principles of the Declaration of Helsinki. The IRB waived the requirement for informed consent for this retrospective study (#2021-0425, approved on 22-Mar-2021).

ORCID iDs

Hyehyun Jeong https://orcid.org/0000-0001-7277-6463
Eunjung Lee https://orcid.org/0000-0001-8598-0498
Jihun Kim https://orcid.org/0000-0002-8694-4365

Supplemental Material

Supplemental material for this article is available online.

References

1. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(3):145-164. doi:10.3322/caac.21601
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):1820-1826. doi:10.1136/gutjnl-2018-317592
3. Saad El Din K, Loree JM, Sayre EC, et al. Trends in the epidemiology of young-onset colorectal cancer: A worldwide systematic review. *BMC Cancer*. 2020;20(1):288. doi:10.1186/s12885-020-06766-9
4. Lui RN, Tsoi KKF, Ho JMW, et al. Global increasing incidence of young-onset colorectal cancer across 5 continents: A joinpoint regression analysis of 1,922,167 cases. *Cancer Epidemiol Biomarkers Prev*. 2019;28(8):1275-1282. doi:10.1158/1055-9965.EPI-18-1111
5. Russo AG, Andreano A, Sartore-Bianchi A, Mauri G, Decarli A, Siena S. Increased incidence of colon cancer among individuals younger than 50 years: A 17 years analysis from the cancer registry of the municipality of Milan, Italy. *Cancer Epidemiol*. 2019;60:134-140. doi:10.1016/j.canep.2019.03.015
6. Rahib L, Wehner MR, Matrisian LM, Nead KT. Estimated projection of US cancer incidence and death to 2040. *JAMA Netw Open*. 2021;4(4):e214708. doi:10.1001/jamanetworkopen.2021.4708
7. Willauer AN, Liu Y, Pereira AAL, et al. Clinical and molecular characterization of early-onset colorectal cancer. *Cancer*. 2019;125(12):2002-2010. doi:10.1002/cncr.31994
8. Khan SA, Morris M, Idrees K, et al. Colorectal cancer in the very young: A comparative study of tumor markers, pathology and survival in early onset and adult onset patients. *J Pediatr Surg*. 2016;51(11):1812-1817. doi:10.1016/j.jpedsurg.2016.07.015
9. Hawk NN, Long T-E, Imam MH, et al. Clinicopathologic features and outcome of young adults with stage IV colorectal cancer. *Am J Clin Oncol*. 2015;38(6):543-549. doi:10.1097/01.coc.0000437899.28701.03
10. Shida D, Ahiko Y, Tanabe T, et al. Shorter survival in adolescent and young adult patients, compared to adult patients, with stage

IV colorectal cancer in Japan. *BMC Cancer*. 2018;18(1):334. doi:10.1186/s12885-018-4241-9

11. Vatandoust S, Price TJ, Ullah S, et al. Metastatic colorectal cancer in young adults: A study from the South Australian population-based registry. *Clin Colorectal Cancer*. 2016;15(1): 32-36. doi:10.1016/j.clcc.2015.07.005
12. Blanke CD, Bot BM, Thomas DM, et al. Impact of young age on treatment efficacy and safety in advanced colorectal cancer: A pooled analysis of patients from nine first-line phase III chemotherapy trials. *J Clin Oncol*. 2011;29(20):2781-2786. doi:10.1200/JCO.2010.33.5281
13. Lieu CH, Renfro LA, de Gramont A, et al. Association of age with survival in patients with metastatic colorectal cancer: Analysis from the ARCAD clinical trials program. *J Clin Oncol*. 2014;32(27):2975-2982. doi:10.1200/JCO.2013.54.9329
14. Kim JE, Chun S-M, Hong YS, et al. Mutation burden and I index for detection of microsatellite instability in colorectal cancer by targeted next-generation sequencing. *J Mol Diagn*. 2019;21(2): 241-250. doi:10.1016/j.jmoldx.2018.09.005
15. Hwang JA, Kim D, Chun S-M, et al. Genomic profiles of lung cancer associated with idiopathic pulmonary fibrosis. *J Pathol*. 2018;244(1):25-35. doi:10.1002/path.4978
16. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Ann Intern Med*. 2007;147(8):573-577. doi:10.7326/0003-4819-147-8-200710160-00010
17. Kanter K, Fish M, Mauri G, et al. Care patterns and overall survival in patients with early-onset metastatic colorectal cancer. *JCO Oncol Pract*. 2021;17:e1846-e1855. doi:10.1200/OP.20.01010
18. Mauri G, Sartore-Bianchi A, Russo AG, Marsoni S, Bardelli A, Siena S. Early-onset colorectal cancer in young individuals. *Molecular Oncol*. 2019;13(2):109-131. doi:10.1002/1878-0261.12417
19. Fu J-F, Huang YQ, Yang J, Yi CH, Chen HL, Zheng S. Clinical characteristics and prognosis of young patients with colorectal cancer in Eastern China. *World J Gastroenterol*. 2013;19(44): 8078-8084. doi:10.3748/wjg.v19.i44.8078
20. Fu J, Yang J, Tan Y, et al. Young patients (≤35years old) with colorectal cancer have worse outcomes due to more advanced disease. *Medicine*. 2014;93(23):e135. doi:10.1097/MD.0000000000000135
21. Lipsyc-Sharf M, Zhang S, Ou F-S, et al. Survival in young-onset metastatic colorectal cancer: Findings from cancer and leukemia group B (Alliance)/SWOG 80405. *J Natl Cancer Inst*. 2021;114: 427-435. doi:10.1093/jnci/djab200
22. Lieu CH, Golemis EA, Serebriiskii IG, et al. Comprehensive genomic landscapes in early and later onset colorectal cancer. *Clin Cancer Res*. 2019;25(19):5852-5858. doi:10.1158/1078-0432.CCR-19-0899
23. Kim JE, Choi J, Sung C-O, et al. High prevalence of TP53 loss and whole-genome doubling in early-onset colorectal cancer. *Exp Mol Med*. 2021;53:446-456. doi:10.1038/s12276-021-00583-1
24. Jorissen RN, Christie M, Mouradov D, et al. Wild-type APC predicts poor prognosis in microsatellite-stable proximal colon cancer. *Br J Cancer*. 2015;113(6):979-988. doi:10.1038/bjc.2015.296
25. Schell MJ, Yang M, Teer JK, et al. A multigene mutation classification of 468 colorectal cancers reveals a prognostic role for APC. *Nat Commun*. 2016;7:11743. doi:10.1038/ncomms11743
26. Brannon AR, Vakiani E, Sylvester BE, et al. Comparative sequencing analysis reveals high genomic concordance between matched primary and metastatic colorectal cancer lesions. *Genome Biol*. 2014;15(8):454. doi:10.1186/s13059-014-0454-7
27. Yaeger R, Chatila WK, Lipsyc MD, et al. Clinical sequencing defines the genomic landscape of metastatic colorectal cancer. *Cancer Cell*. 2018;33(1):125-136. doi:10.1016/j.ccell.2017.12.004
28. Andre T, Shiu KK, Kim TW, et al. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. *N Engl J Med*. 2020;383(23):2207-2218. doi:10.1056/NEJMoa2017699
29. Schrock AB, Ouyang C, Sandhu J, et al. Tumor mutational burden is predictive of response to immune checkpoint inhibitors in MSI-high metastatic colorectal cancer. *Ann Oncol*. 2019; 30(7):1096-1103. doi:10.1093/annonc/mdz134
30. Valero C, Lee M, Hoen D, et al. Response rates to anti-PD-1 immunotherapy in microsatellite-stable solid tumors with 10 or more mutations per megabase. *JAMA Oncol*. 2021;7:739. doi: 10.1001/jamaoncol.2020.7684