Clinicopathological and Molecular Characteristics of Early-Onset vs Late-onset Colorectal Cancer according to Tumor Location

Yongle Chen

Sun Yat-sen University Sixth Affiliated Hospital

Zexian Chen

Sun Yat-sen University Sixth Affiliated Hospital

Juanni Huang

Guangzhou Medical University

Jiancong Hu

Sun Yat-sen University Sixth Affiliated Hospital

Xiaowen He

Sun Yat-sen University Sixth Affiliated Hospital

Ping Lan

Sun Yat-sen University Sixth Affiliated Hospital

Xiaosheng He (✉ hexsheng@mail.sysu.edu.cn)

Sun Yat-sen University Sixth Affiliated Hospital

Research article

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Abstract

Background

The incidence of early-onset colorectal cancer (EOCRC) is rapidly increasing worldwide in decade when screening of colorectal cancer (CRC) is more prevalent. The clinicopathological and molecular characteristics of EOCRC have not yet been clarified. This study aims to evaluate clinicopathological and molecular features including status of deficiencies of mismatch repair (dMMR), mutation of PIK3CA, BRAF and KRAS among EOCRC and late-onset colorectal cancer (LOCRC) patients according to different tumor locations.

Methods

We identified CRC patients from a prospectively maintained CRC database between January 2015 and December 2018 at the Sixth Affiliated Hospital of Sun Yat-sen University. The clinicopathological and molecular characteristics including dMMR, mutation of PIK3CA, BRAF and KRAS were compared between EOCRC and LOCRC. The relationships according to different tumor locations were assessed.

Results

Totally 4468 patients, including 947 EOCRC patients and 3521 LOCRC patients, were analyzed in this study. Compared with LOCRC patients, EOCRC patients were more likely to have status of dMMR (odds ratio [OR], 2.52; 95% confidence interval [CI], 2.05-3.10; $P<0.001$), regardless of tumor location, so were loss of MSH2 and MSH6 (OR, 4.31; 95% CI, 2.86-6.48; $P<0.001$; OR, 3.40; 95% CI, 2.42-4.76; $P<0.001$, respectively). Loss of MLH1 and PMS2 were detected more frequently in EOCRC overall (OR, 2.11; 95% CI, 1.55-2.87; $P<0.001$; OR, 1.83; 95% CI, 1.42-2.35; $P<0.001$, respectively), but only in left-side and right-side colon rather than in rectum. EOCRC patients were more likely to be detected with mutation of PIK3CA (OR, 1.24; 95% CI, 1.01-1.53; $P=0.041$), which only trended to exist in the left-side colon (OR, 1.51; CI, 0.98-2.33; $P=0.06$), but not in the right-side colon or rectum. No significant difference was found for BRAF or KRAS mutation, but mutation of KRAS was more frequently found in left-side colon (OR, 1.34; CI, 1.02-1.77; $P=0.04$) among EOCRC patients.

Conclusions

Status of dMMR, mutation of PIK3CA, BRAF and KRAS were different between EOCRC and LOCRC patients according to different tumor locations, which implied that EOCRC might be a unique subgroup of CRC patients. Further investigations of molecular and genetic differences should be performed to help define new diagnosing and therapeutical strategies for EOCRC patients.

Introduction

Colorectal cancer (CRC) is the third most common and the second most lethal cancer worldwide [1], which has been found to have a higher incidence with increasing age. Due to benefits of CRC screening, CRC incidence has declined overall or been stable in developed countries in the last decades. In contrast, the incidence of CRC among individuals younger than 50 years of age (early-onset CRC, EOCRC) is on a significant rise [2, 3]. It is estimated that around 11% of colon cancers and 18% of rectal cancers occur in individuals younger than 50 years of age [4]. Previous studies suggested that EOCRC patients might be a specific subgroup that tended to have a higher prevalence of low-grade tumor differentiation, to exhibit an advanced stage, and to present with or develop to metastatic disease [5]. However, whether EOCRC patients have a distinct biological behavior remains controversial.

Status of mismatch repair (MMR) genes and mutation of PIK3CA, BRAF and KRAS were important biomarkers to evaluate CRC. Up to 15-20% of EOCRC has a hereditary component [6]. The underlying pathogenesis may relate to presence of germ-line mutations in MMR genes, which results in microsatellite instability (MSI) or deficiencies of mismatch repair genes (dMMR) [7]. dMMR could be found in 15% of sporadic CRC, mainly due to an epigenetic inactivation of MLH1 [8]. Palomba G et al. reported an overall mutation rate were 35.6 % for KRAS, 2.1 % for BRAF, and 14.3 % for PIK3CA gene [9]. A comprehensive genetic characterization of EOCRC in a large cohort is lacking, thus the difference of dMMR status, mutation of KRAS, BRAF, PIK3CA genes between EOCRC and LOCRC patients still needs further research, as well as their difference according to different tumor locations. To fill this knowledge gap, we attempted to investigate the clinicopathological and molecular characteristics between EOCRC and LOCRC patients, and their difference according to different tumor locations, therefore stratifying CRC patients by holding up the age of onset and tumor location.

Materials And Methods

Patients Selection

This study was in accordance with the Helsinki Declaration and approved by the institutional review board of the Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China. Patients diagnosed with CRC who underwent surgery for colorectal adenocarcinoma from January

2015 to December 2018 were identified at the Sixth Affiliated Hospital of Sun Yat-sen University from a prospectively maintained CRC database. Exclusion criteria were: (1) patients younger than 18 or older than 90 years; (2) recurrent CRC; (3) patients with multiprimary cancer; (4) patients with substantial missing data. EOCRC patients were defined as those diagnosed with CRC under age of 50 years old in this study. Data of clinicopathological and molecular variables were collected including age, gender, body mass index, and information of tumor (location, stage, differentiation and molecular testing). After manual review, there were total 4468 patients included in this study (947 EOCRC cases and 3521 LOCRC cases). Flow chart of patient selection was shown in Figure 1.

Definition of variables

Tumor staging was performed according to the 8th Edition of American Joint Committee on Cancer TNM staging system. Tumor differentiation was categorized as well differentiated, moderately differentiated, poorly differentiated, undifferentiated carcinoma, mucinous carcinoma, or signet-ring cell tumor. The primary tumor location site was categorized as right-side colon if the tumor was located above the splenic flexure (including cecum, ascending colon and transverse colon), and left-side colon if it was located at or below the splenic flexure and above rectum (including descending colon and sigmoid colon), and rectum.

Status of MMR were examined using immunohistochemical staining for MLH1, MSH2, MSH6, and PMS2 protein. Cases with complete nuclear loss of MMR expression in invasive tumor cells but with retained expression in inflammatory cells and/or adjacent normal tissue as positive controls were considered MMR deficiency. Mutation of PIK3CA, BRAF and KRAS genes were examined using polymerase chain reaction, including mutation of exon9 and exon20 of PIK3CA, BRAF V600E and exon2, exon3 and exon4 of KRAS.

Statistical analysis

SPSS were used for data analysis. Descriptive statistics for measurements are expressed as mean value $\pm$ standard deviation, and t-tests or Wilcoxon rank sum tests were used to compare according to the data type. The relationships according to different tumor locations were assessed using binary logistic regression models. Results were considered statistically significant with two-sided p-value < 0.05 .

Results

Clinicopathological characteristics

A total of 4468 patients with CRC were included in this study, among whom 947 patients (21.2%) were EOCRC and 3521 patients (78.8%) were LOCRC. The average age at diagnosis was 59.6 ± 12.8 years overall, and 41.2 ± 6.8 and 64.5 ± 9.0 in patients with EOCRC and LOCRC, respectively. 2730 (61.1%) patients were male and 1738 (39.1%) were female, with a gender ratio of 1.53. Most of the patients were with stage II (1754, 39.3%) and III (1481, 33.2%) tumors. About one half (47.9%) of tumors were located in rectum. Data of clinicopathological characteristics of patients were shown in Table 1.

Status of dMMR, mutation of PIK3CA, BRAF and KRAS

Overall, 10.2% patients had status of dMMR; while 12.2%, 2.84% and 45.7% patients were detected with PIK3CA mutation, BRAF mutation and KRAS mutation, respectively. Compared with LOCRC patients, EOCRC patients were more likely to have dMMR status (18.1% vs. 8.04%, odds ratio [OR], 2.52; confidence interval [CI], 2.05-3.10; $P < 0.001$). Negative status of MLH1 (OR, 2.11; CI, 1.55-2.87; $P < 0.001$), MSH2 (OR, 4.31; CI, 2.86-6.48; $P < 0.001$), MSH6 (OR, 3.40; CI, 2.42-4.76; $P < 0.001$), PMS2 (OR, 1.83; CI, 1.42-2.35; $P < 0.001$) were all observed more frequently in patients with EOCRC. EOCRC patients were more likely to detected with mutation of PIK3CA (14.1% vs. 11.7%, OR, 1.24; CI, 1.01-1.53; $P = 0.041$), especially at exon20 (OR, 1.88; CI, 1.36-2.60; $P < 0.001$). No significant difference was found for BRAF or KRAS mutation (Table 2).

Status of dMMR, mutation of PIK3CA, BRAF and KRAS in different tumor locations

Compared with LOCRC patients, status of dMMR was detected more frequently in EOCRC, regardless of location of tumor, so were loss of MSH2 and MSH6. Loss of MLH1 and PMS2 were detected more frequently in EOCRC in colon including both left side (OR, 3.64; CI, 1.85-7.16; $P < 0.001$; and OR, 2.50; CI, 1.44-4.35; $P = 0.001$, respectively) and right side (OR, 1.85; CI, 1.23-2.78; $P = 0.003$; and OR, 1.97; CI, 1.38-2.82; $P < 0.001$, respectively), but not in rectum.

As mentioned above, EOCRC patients were more likely to detected with mutation of PIK3CA, which only trended to exist in left-sided colon (OR, 1.51; CI, 0.98-2.33; $P = 0.06$), but not in right-sided colon or rectum. Overall, no significant difference was found for BRAF or KRAS mutation between EOCRC and LOCRC, but mutation of KRAS was more frequently in EOCRC in left-sided colon (OR, 1.34; CI, 1.02-1.77; $P = 0.04$) rather than in right-sided colon or rectum, especially mutation at exon 2 (OR, 1.60; CI, 1.21-2.12; $P = 0.001$) (Table 3).

Discussion

It is now recognized that the incidence of EOCRC is increasing rapidly at a global scale [2-4]. Mounting evidence indicates that EOCRC has unique molecular profiles, which might influence disease outcomes and response to therapy [10].

With regard to MMR status, recent studies found that dMMR was more prevalent in EOCRC patients. Pan Li et al. [11] reported a higher incidence of dMMR in younger group of patients (13.8%) versus the middle-aged (12.2%) or older-aged patients (7.9%) ($P < 0.001$), and young CRC patients with dMMR had higher OS than young patients with pMMR ($P = 0.03$). R Gryfe et al. [12] also reported a high-frequency of dMMR in 17% of colorectal cancers in EOCRC patients. Likewise, in this study, we found that about 10.2% patients with CRC had status of dMMR on the whole, and it was detected more frequently in EOCRC patients (18.1%) versus LOCRC patients (8.0%) (odds ratio [OR], 2.52; 95% confidence interval [CI], 2.05-3.10; $P < 0.001$). What's more, in this study, we found that dMMR rate was significant different according to tumor location between EOCRC and LOCRC patients. Compared with LOCRC patients, EOCRC patients were more likely to have status of dMMR regardless of location of tumor, so were loss of MSH2 and MSH6 (OR, 4.31; CI, 2.86-6.48; $P < 0.001$; OR, 3.40; CI, 2.42-4.76; $P < 0.001$, respectively). Loss of MLH1 and PMS2 were detected more frequently in EOCRC overall (OR, 2.11; CI, 1.55-2.87; $P < 0.001$; OR, 1.83; CI, 1.42-2.35; $P < 0.001$, respectively), but only in colon including both left side and right side rather than in rectum.

Mutation of PIK3CA, BRAF and KRAS is mainly focus on CRC patients with recurrence or metastasis. They are important potential biomarkers for prognosis as well as targeted therapies [13, 14]. Though their influence on therapeutic strategy in non-recurrent or non-metastatic CRC was unknown, frequency of such mutation and the association with clinicopathological variables were more and more reported in recent years [15-17].

In a meta-analysis of PIK3CA by Shuofei Yang, et al, forty-four studies enrolling 17621 patients were eligible and the rate of PIK3CA mutation was 12.9% and was associated with proximal tumor location [18]. In the present study, mutations of PIK3CA was detected in 12.2% patients overall, and more likely in EOCRC than LOCRC (OR, 1.24; CI, 1.01-1.53; $P = 0.041$), but not associated with tumor location significantly.

As previously reported, mutation of KRAS is an early event in the carcinogenesis of CRC and its incidence in CRC patients is about 30% to 50% [19]. In our study, the incidence of KRAS mutation was 46.8%, which was similar to those in studies of Eastern and Western populations [15]. Most previous studies reported a higher incidence of KRAS mutations in EOCRC patients, which may due to KRAS mutations usually associate with more advanced tumor stage in CRC patients [20]. Pillozzi E et al. [19] reported that the EOCRC with left-sided tumors showed KRAS mutation in 43% of cases; in contrast, in the LOCRC, KRAS mutation was observed in 18% of cases. Gunal et al. [20] showed a very high incidence of KRAS mutations in patients younger than 40 years compared with those older than 40 years (66.7% and 36%, respectively). In our study, there was no significant difference of KRAS mutations incidence between EOCRC and LOCRC patients, but mutation of KRAS was more frequently in EOCRC than LOCRC in left-sided colon (OR, 1.34; CI, 1.02-1.77; $P = 0.04$) rather than in right-sided colon or rectum.

Frequency of BRAF mutation was 10.8% in meta-analysis with about 12 thousand patients, and was found associated with advanced TNM stage, poor differentiation [21]. In our study, we didn't find a significant difference for BRAF mutation in age and tumor location.

Conclusion

In this retrospective study of patients with EOCRC vs LOCRC, we found status of dMMR, mutation of PIK3CA and KRAS were different between EOCRC and LOCRC patients according to different tumor locations, which implied that EOCRC may be a unique subgroup of CRC patients. Further investigations of molecular and genetic differences should be performed to help define new diagnosing and therapeutical strategies for EOCRC patients.

Abbreviations

EOCRC, early-onset colorectal cancer; CRC, colorectal cancer; dMMR, deficiencies of mismatch repair; LOCRC, late-onset colorectal cancer; OR, odds ratio; CI, confidence interval; MSI, microsatellite instability.

Declarations

Ethics approval and consent to participate

This study was in accordance with the Helsinki Declaration and approved by the institutional review board of the Sixth Affiliated Hospital of Sun Yat-sen University.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All the authors contributed to the conception and design of the study. YLC, JNH and ZXC contributed to the collection of data. JCH and XWH contributed to the analysis and interpretation of the data. YLC and ZXC contributed to drafting the manuscript. PL and XSH contributed to critical revision of the manuscript for important intellectual content. All of the authors approved the final draft of the article.

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Disclosure Statement

The authors declare that there is no conflict of interest.

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Tables

Table 1. Clinicopathological information

Variable	Overall	EOCRC	LOCRC
No.	4468	947(21.2%)	3521(78.8%)
Average age (year)	59.6± 12.8	41.2± 6.8	64.5± 9.0
Gender			
Male	2730 (61.1%)	520 (54.9%)	2210 (62.8%)
Female	1738 (39.9%)	427 (45.1%)	1311 (37.2%)
BMI (kg/m ²)	22.6± 3.3	22.4± 3.5	22.6± 3.3
≤18	339 (7.59%)	86 (9.08%)	253 (7.19%)
18-24.9	3171 (71.0%)	651 (68.7%)	2520 (71.6%)
25-29.9	859 (19.2%)	191 (20.2%)	668 (19.0%)
≥30	99 (2.22%)	19 (2.01%)	80 (2.27%)
T stage			
0	15 (0.34%)	3 (0.32%)	12 (0.34%)
1	172 (3.85%)	27 (2.85%)	145 (4.12%)
2	577 (12.9%)	108 (11.4%)	469 (13.3%)
3	3100 (69.4%)	664 (70.1%)	2436 (69.2%)
4	604 (13.5%)	145 (15.3%)	459 (13.0%)
N stage			
0	2494 (55.8%)	482 (50.9%)	2012 (57.1%)
1	1376 (30.8%)	276 (29.1%)	1100 (31.2%)
2	598 (13.4%)	189 (20.0%)	409 (11.6%)
M stage			
0	3807 (85.2%)	792 (83.6%)	3015 (85.6%)
1	661 (14.8%)	155 (16.4%)	506 (14.4%)
TNM stage			
0	14 (0.31%)	2 (0.21%)	12 (0.34%)
I	558 (12.5%)	100 (10.6%)	458 (13.0%)
II	1754 (39.3%)	343 (36.2%)	1411 (40.1%)
III	1481 (33.2%)	347 (36.6%)	1134 (32.2%)
IV	661 (14.8%)	155 (16.4%)	506 (14.4%)
Tumor location			
Rectum	2138 (47.9%)	426 (45.0%)	1712 (48.6%)
Left-sided colon	1267 (28.4%)	271 (28.6%)	996 (28.3%)
Right-sided colon	1063 (23.8%)	250 (26.4%)	813 (23.1%)

Abbreviation: EOCRC, early-onset colorectal cancer; LOCRC, late-onset colorectal cancer.

Table 2. Comparisons on status of dMMR, mutation of PIK3CA, BRAF and KRAS between EOCRC and LOCRC patients

	Overall (n=4468)	EOCRC (n=947)	LOCRC (n=3521)	OR (95% CI)	P value
dMMR	454 (10.2%)	171 (18.1%)	283 (8.04%)	2.52 (2.05, 3.10)	0.001*
MLH1 negative	187 (4.19%)	66 (6.97%)	121 (3.44%)	2.11 (1.55, 2.87)	0.001*
MSH2 negative	95 (2.13)	50 (5.28%)	45 (1.28%)	4.31 (2.86, 6.48)	0.001*
MSH6 negative	142 (3.18)	66 (6.97%)	76 (2.16%)	3.40 (2.42, 4.76)	0.001*
PMS2 negative	304 (6.80)	97 (10.2%)	207 (5.88%)	1.83 (1.42, 2.35)	0.001*
PIK3CA mutation	546 (12.2%)	134 (14.1%)	412 (11.7%)	1.24 (1.01, 1.53)	0.041*
exon9 mutation	376 (8.42%)	77 (8.13%)	299 (8.49%)	0.95 (0.73, 1.24)	0.722
exon20 mutation	173 (3.87%)	57 (6.02%)	116 (3.29%)	1.88 (1.36, 2.60)	0.001*
BRAF mutation	127 (2.84%)	28 (2.96%)	99 (2.81%)	1.05 (0.69, 1.61)	0.812
KRAS mutation	2041 (45.7%)	427 (45.1%)	1614 (45.8%)	0.97 (0.84, 1.12)	0.768
exon2 mutation	1743 (39.0%)	362 (38.2%)	1381 (39.2%)	0.96 (0.83, 1.11)	0.577
exon3 mutation	103 (2.31%)	20 (2.11%)	83 (2.36%)	0.89 (0.55, 1.46)	0.654
exon4 mutation	202 (4.52%)	48 (5.07%)	154 (4.37%)	1.17 (0.84, 1.63)	0.363

Abbreviation: EOCRC, early-onset colorectal cancer; LOCRC, late-onset colorectal cancer; OR, odds ratio; CI, confidence interval. * P value with statistic significance.

Table 3. Comparisons on status of dMMR, mutation of PIK3CA, BRAF and KRAS between EOCRC and LOCRC patients according to different tumor locations

	Rectum (n=2138)				Left-sided colon (n=1267)				Right-sided colon (n=1063)			
	≥50 (n=1712)	<50 (n=426)	OR (95% CI)	P value	≥50 (n=996)	<50 (n=271)	OR (95% CI)	P value	≥50 (n=813)	<50 (n=250)	OR (95% CI)	P value
dMMR	87	38	1.83 (1.23, 2.72)	0.003*	48	39	3.32 (2.13, 5.19)	<0.001*	148	94	2.71 (1.98, 3.70)	<0.001*
MLH1 negative	25	8	1.29 (0.58, 2.88)	0.53	18	17	3.64 (1.85, 7.16)	<0.001*	78	41	1.85 (1.23, 2.78)	0.003*
MSH2 negative	7	13	7.67 (3.04, 19.3)	<0.001*	5	14	10.8 (3.85, 30.3)	<0.001*	33	23	2.39 (1.38, 4.16)	0.002*
MSH6 negative	13	19	6.10 (2.99, 12.5)	<0.001*	13	13	3.81 (1.75, 8.32)	0.001*	50	34	2.40 (1.51, 3.81)	<0.001*
PMS2 negative	65	17	1.05 (0.61, 1.82)	0.85	34	22	2.50 (1.44, 4.35)	0.001*	108	58	1.97 (1.38, 2.82)	<0.001*
PIK3CA mutation	156	41	1.06 (0.74, 1.53)	0.74	81	32	1.51 (0.98, 2.33)	0.06	175	61	1.18 (0.84, 1.64)	0.34
exon9 mutation	114	23	0.80 (0.50, 1.27)	0.34	60	25	1.59 (0.97, 2.58)	0.06	125	29	0.72 (0.47, 1.11)	0.14
exon20 mutation	43	18	1.71 (0.98, 3.00)	0.06	21	7	1.23 (0.52, 2.93)	0.64	52	32	2.15 (1.35, 3.42)	0.001*
BRAF mutation	17	7	1.67 (0.69, 4.04)	0.26	16	4	0.92 (0.30, 2.77)	0.88	66	17	0.83 (0.48, 1.44)	0.50
KRAS mutation	822	185	0.83 (0.67, 1.03)	0.09	343	112	1.34 (1.02, 1.77)	0.04*	449	132	0.91 (0.68, 1.20)	0.50
exon2 mutation	709	155	0.81 (0.65, 1.01)	0.06	282	105	1.60 (1.21, 2.12)	0.001*	390	102	0.75 (0.56, 1.00)	0.05
exon3 mutation	32	10	1.26 (0.62, 2.59)	0.53	28	4	0.52 (0.18, 1.49)	0.22	23	6	0.84 (0.34, 2.10)	0.72
exon4 mutation	84	20	0.95 (0.58, 1.57)	0.85	33	4	0.44 (0.15, 1.24)	0.12	37	24	2.23 (1.30, 3.80)	0.003*

Abbreviation: EOCRC, early-onset colorectal cancer; LOCRC, late-onset colorectal cancer; OR, odds ratio; CI, confidence interval. * P value with statistic significance.

Figures

Figure 1

Flow chart of patient selection