



Research Article

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Young-Onset Colorectal Carcinoma: Is This A Single Entity or A Two Age Group with Different Pathological Findings and Molecular Profiles?

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Abstract

Context: Although the national incidence of colorectal cancer (CRC) has decreased in recent years, mortality has increased among those younger than 50 years. While CRC has been widely studied, there have been few studies analyzing specific pathologic parameters in patients with young-onset CRC (YO-CRC). YO-CRC is one of the hallmarks of hereditary CRC syndromes.

Objective: The primary aim of this study was to identify the clinical, pathological, and molecular features of YO-CRCs.

Design: All patients with a diagnosis of YO-CRC treated surgically at our institution between August 2016 and February 2020 were included in our study. The age distribution, race, ethnicity, history of hereditary cancer syndromes, tumor location, grade, stage, size, and molecular findings were analyzed. We divided the patients into four groups according to the race/ethnicity identified in our electronic medical record (White/Non-Hispanic or Latino (W/N-HL), Black/Non-Hispanic or Latino (B/N-HL), Asian/Non-Hispanic or Latino (A/N-HL), and Other/Hispanic/Latino (O/HL)).

Results: Twenty-six patients with CRC were included. B/N-HL and W/N-HL patients formed the largest groups. Most of the cases were identified in B/N-HL females. The tumors measured 5-10 cm on average, were located in the rectum, were well-to-moderately differentiated, presented at advanced stages, and were microsatellite stable (Table 1).

Conclusions: The majority of the cases with YO-CRC were sporadic CRCs diagnosed at advanced stage-rectal carcinomas in B/N-HL and W/N-HL. YO-CRCs are a subset of CRCs with distinct clinical, pathological and molecular behaviors.

Keywords: colorectal cancer, young-onset, hereditary, molecular.

Introduction

Although the national incidence of colorectal cancer (CRC) has decreased in recent years, CRC remains the fourth most common cancer in both men and women and the third most common cause of cancer-related death in the United States [1]. Colon cancer accounts for 8.8% of all carcinomas, with 147,950 new cases per year and 53,200 deaths [1]. Most of the cases are diagnosed in patients aged 65 years and older [1]. Young-onset colorectal carcinoma is defined as a CRC diagnosed before 50 years of age [2]. In the USA, 11% of

colon cancers and 18% of rectal cancers have a young-onset [1]. In 2010, young-onset colorectal cancer (YO-CRC) accounted for 4.8% of the colon cancers [3]. Over the past 15 years, CRC incidence and mortality rates in adults aged 50 years and older have declined by 32% and 34%, respectively. In contrast, mortality has increased among those younger than 50 years, and there has been a rising incidence of CRC in successive age cohorts born between 1950 and 1990 [4]. Age-mortality rates from 2000 to 2017 show an increase in rates from 1.6 per 100,000 to 1.8 per 100,000 [1].



Regardless of the age of presentation, CRC incidence and mortality remain higher among blacks than among any other racial/ethnic group, with incidence rates 20% higher and mortality rates 40% greater than those among W/N-HL [4]. According to the Surveillance Epidemiology and End Results program's cancer statistics (SEER), African Americans (AA) show the highest incidence (51.3 per 100,000 in males and 38.2 per 100,000 in females) and mortality rates (23.2 per 100,000 in males and 15.2 per 100,000 in females) of CRC. [1]. Using data from the SEER program, Murphy et al found racial disparities in the incidence of young-onset colorectal carcinoma (YO-CRC) and patient survival for colon cancer but a minimal difference for rectal cancer. They concluded that increases in YO-CRC have been due to increases in rectal cancer, especially in whites [4,5]. Although Blacks are one of the most commonly affected groups, the White and Hispanic populations have shown a significant increase in incidence rate of CRC from 2013 to 2017 (1.7 in Hispanics, 1.3 in Whites, and 0.3 in AA) [1].

Murphy et al found that, compared with Whites, Blacks had smaller increases in relative survival for proximal tumors and greater increases for rectal cancer [5]. In addition, Ellis et al. found rising incidence rates of CRC among young adults and Southeast Asians of screening age [6]. In the USA, the increase in YO-CRC diagnoses has been observed in patients aged 20-35 years [3]. By 2030, it is predicted that the incidence rate of CRC will double in patients younger than 35, and the highest increase is expected for rectal cancers [3]. Approximately 20% of the YO-CRCs are associated with hereditary cancer syndromes [7]. The most frequent syndromes are Lynch syndrome and familial adenomatous polyposis [3]. YO-CRCs are more commonly identified in the rectum and left colon, are poorly differentiated, have mucinous and signet-ring cell features, and present at advanced stages [7]. The literature has contradicting data about the molecular findings of YO-CRCs. Most studies have revealed a lower prevalence of KRAS mutations (4-31%), but other studies have reported similar (35-39%) or higher (54%) prevalence than CRCs in patients aged 50 years and older [3].

The prevalence of BRAF V600E in YO-CRCs is similar to that in older patients (0-19%) [3]. NRAS mutations are identified in 1% of the YO-CRCs [3]. Several studies have reported that the nonhereditary YO-CRCs are microsatellite stable (MSS), and have a lower frequency of BRAF mutations, a lower frequency of the CpG island methylator phenotype, and a greater frequency of hypomethylation of LINE than older-onset MSS CRCs [7]. A retrospective study performed by Willauer et al in 2019 showed that YO-CRCs are more likely to have microsatellite instability, synchronous metastatic disease, primary tumors in the distal colon or rectum, and fewer BRAF V600E mutations compared to older patients [8]. A subset of patients aged 18-29 had fewer APC

mutations and increased prevalence of signet ring cell morphology compared to patients younger than 50 years. In patients younger than 40 years, CMS1 was the most common subtype [8]. Survival is worst in patients younger than 30 years old. In contrast, survival is comparable or even better among patients age 40 to 50 compared to those older than 50. Treatment modalities for YO-CRC are similar to those for CRC in patients older than 50 years [3].

Materials and Methods

Patients

After institutional review board approval, all patients with a diagnosis of carcinoma of the colorectum treated surgically at the University of Illinois Hospital and Health and Sciences System (UIH) between August 2016 and February 2020 were included in our study. A total of twenty-six patients younger than 50 years of age had surgical resection during this period. Only patients with a diagnosis of adenocarcinoma of the colon and/or rectum were included. We excluded patients with other histologic subtypes of colon cancer, sarcomas, lymphomas, metastatic disease, unknown race/ethnicity, as well as patients younger than 18 and patients 50 years of age or older. The patients' clinical information was gathered from the electronic medical record (EMR) system at UIH. We divided the patients into four groups according to the race/ethnicity identified in our EMR (White/Non-Hispanic or Latino (W/N-HL), Black/Non-Hispanic or Latino (B/N-HL), Asian/Non-Hispanic or Latino (A/N-HL), and Other/Hispanic or Latino (O/HL)).

Data collection

The pathology reports and the EMRs of the 26 patients were reviewed. The collected data included age, sex, race/ethnicity, location and size of the tumor, histologic grade, stage, size of tumor, presence of treatment effect, and molecular findings. Demographic and clinical data such as age, race and ethnicity, past medical history of hereditary cancer syndromes, and history of presurgical treatment were retrieved from the EMR database. SSSYoung-onset colorectal carcinoma was defined as a CRC diagnosed before 50 years of age. The location of the carcinomas was categorized as right-sided, left-sided non-rectal, or left-sided rectal. Right-sided tumors were defined as those proximal to the splenic flexure. Left-sided tumors were subsequently subdivided into left-sided non-rectal tumors (included tumors located from the splenic flexure proximal to the sigmoid colon) and left-sided rectal tumors (located from the sigmoid to the anal canal).

Primary and secondary outcomes

The primary aim of this study was to identify the clinical, pathological, and molecular features of YO-CRCs. Secondary aims of this study were to identify the percentage of patients with YO-CRC, the molecular abnormalities, percentage of cases with hereditary

cancer syndromes, racial/ethnic disparities, age distribution, the location of the tumor, histologic grade, histologic type, tumor size, stage at presentation, and presence of treatment effect in rectal carcinomas in the population of patients who consult to our institution.

Statistical analysis

Statistical analysis was performed using different methods depending on the variable to be analyzed. The ANOVA procedure

was used for the analysis of race effect on tumor sizes. Fisher's exact test was used to analyze the statistical differences in age and tumor location. A two-sample t-test was used to analyze the statistical differences in tumor size, age, and sex.

Results

Baseline characteristics

Baseline characteristics are summarized in Table 1. Twenty-six patients were included in the study (n=26) Table 1.

Table 1: Young-Onset CRC.

	Age	Sex	Race/ Ethnicity	Site	Grade	Stage	Size (cm)	Treatment effect	Molecular Findings
1	23	F	O/HL	Rectum	G1	IIIC	5-10	P	MSS; no BRAF, KRAS or NRAS mutations.
2	24	M	O/HL	Rectum	G1	I	3-4	P	MSS; APC mutation; no other tests done
3	30	F	W/N-HL	Left	G1	IV	1-2	N/A	MSS; no BRAF; KRAS codon 12
4	33	F	B/N-HL	Rectum	G4	IIC	5-10	Ab	MSI (MLH1, PMS2); no BRAF, V600E, or KRAS
5	33	F	B/N-HL	Rectum	G4	IV	5-10	Ab	MSS; no BRAF, KRAS or NRAS mutations.
6	37	F	B/N-HL	Right	G2	IIC	5-10	N/A	MSS; no BRAF; KRAS p.A146T
7	37	F	O/HL	Rectum	G1	IV	3-4	P	MSI (MSH2, MSH6); NO BRAF V600E
8	38	F	W/N-HL	Rectum	G2	IV	5-10	U	MSS; no BRAF, KRAS or NRAS mutations.
9	38	M	O/HL	Left	G2	IV	5-10	N/A	MSI; no BRAF or NRAS mutations. KRAS codon 13 mut
10	39	F	B/N-HL	Rectum	G1	IV	<1	P	MSS; no BRAF, KRAS or NRAS mutations.
11	39	F	W/N-HL	Left	G1	IIIC	>10	N/A	MSS; no BRAF; KRAS codon 13
12	39	M	B/N-HL	Rectum	N/A	0	0	P	MSS; no BRAF V600E; KRAS codon 13 in liver mets
13	40	M	B/N-HL	Right	G1	IV	>10	N/A	MSI-H; No BRAF V600E; KRAS codon 13
14	41	M	O/HL	Rectum	G2	IV	CNBD	P	MSS; no BRAF, KRAS or NRAS mutations.
15	42	M	W/N-HL	Right	G1	I	2-3	N/A	MSS; no BRAF, KRAS or NRAS mutations.
16	42	F	W/N-HL	Rectum	N/A	0	0	P	No test done
17	45	M	B/N-HL	Rectum	G1	IV	2-3	P	MSS; no BRAF or KRAS. NRAS mutation.
18	45	M	A/N-HL	Rectum	G1	I	<1	P	MSS; no BRAF, KRAS or NRAS mutations.
19	46	M	A/N-HL	Right	G1	I	<1	N/A	MSS; no BRAF, KRAS or NRAS mutations.
20	46	M	B/N-HL	Right	G1	IV	3-4	N/A	MSS; no BRAF; KRAS codon 12
21	47	F	O/HL	Rectum	G2	IIIB	5-10	Ab	MSS; no BRAF; KRAS codon 12
22	47	F	B/N-HL	Left	G1	IV	2-3	P	MSS; no BRAF, KRAS or NRAS mutations.
23	48	M	W/N-HL	Left	G1	IV	1-2	N/A	MSS; no BRAF, KRAS or NRAS mutations.
24	48	M	O/HL	Right	G2	IV	5-10	N/A	MSS; no BRAF, KRAS or NRAS mutations.
25	49	M	B/N-HL	Left	G2	IV	4-5	N/A	MSS; no BRAF, KRAS or NRAS mutations.
26	49	F	W/N-HL	Rectum	G1	IV	<1	Ab	MSS; no other tests done

F: Female; M: Male; G: Grade; cm: Centimeter; P: Present; A: Absent; N/A: Not Applicable; Ab: Absent; U: Unknown; CNBD: Cannot be determined O/HL: Other/Hispanic or Latino; W/NH-L: White/Non-Hispanic or Latino; B/NH-L: Black/Non-Hispanic or Latino; A/NH-L: Asian/Non-Hispanic or Latino
MSS: Microsatellite stable; MSI: Microsatellite instability; BRAF: B-Raf protein; MLH1: MutL homolog 1; PMS2: PMS1 homolog 2; MSH2: MutS homolog 2; MSH6: MutS homolog 6; KRAS: K-Ras protein; NRAS: N-Ras protein.

Age: The mean age was 40.1 years old. The age ranged from 23 to 49 years old. CRCs were resected at an earlier age in the O/N-HL and B/N-HL populations (mean age 36.9 and 40.8 years old) than

in the W/N-HL and A/HL populations (41.1 and 45.5 years old respectively). CRC was detected earlier in the rectum (mean age: 38.2 years old) than in the left (mean age: 41.8 years old) or the

right colon (mean age: 43.1 years old). To test for a statistically significant age difference among the four racial/ethnic groups, an analysis of variance (ANOVA) on ages was conducted at the level of $\alpha = 0.05$. There was no statistically significant age difference when comparing the four groups (Fisher's p-value 0.175).

Sex: Thirteen patients were female (50%); thirteen patients were male (50%).

Race/ethnicity: Ten patients were B/N-HL (38.5%), seven patients were W/N-HL (26.9%), seven patients were O/HL (26.9%), and two patients were A/N-HL (7.7%). No American Indian/Alaska Natives were identified.

Tumor site: Fourteen cases were located in the rectum (53.8%), 6 cases in the right colon (23.1%), and six in the left colon (23.1%).

Histologic grade: The most common histologic grades were grade 1 (n=15; 57.7%) and 2 (n=7; 26.9%). Only 2 cases were classified as grade 4 or undifferentiated (7.7% each).

Stage: The most common pathologic stage was IV (n=15; 57.7%). Two cases were diagnosed as stage 0 (7.7%), four as stage I (15.4%), two as stage IIC (7.7%), one as stage IIIB (3.8%), and two as stage IIIC (7.7%). Of the 15 stage IV cases, these tumors were more frequent in B/N-HL (n=7; 46.7%) than in W/N-HL (n=4; 26.7%), O/HL (n=4; 26.7%) or A/N-HL (n=0). Stage IV YO-CRC were more frequently identified in the rectum (n=7; 46.7%) than in the left colon (n=5; 33.3%) or right colon (n=3; 20.0%).

Tumor size: The tumor size ranged from less than 1 centimeter (cm) to more than 10 cm. Eight cases measured 5-10 centimeters (cm) (30.8%) and only two cases measured more than 10 cm (7.7%). Most of the rectal carcinomas status post treatment measured between 0 to 3cm. The remainder of the tumors measured 4-5 cm (n=1), 3-4 cm (n=3), and 1-2 cm (n=2). In one case the tumor size could not be determined. Of the fourteen rectal carcinomas, treatment effect was present in 9 cases (64.3%), absent in 4 cases (28.6%), and unknown in 1 case (7.1%). In the cases with treatment effect, partial response was the most common tumor regression score identified (n=6; 23%). Two cases showed complete response (7.6%) and two cases showed poor or no response (7.6%).

Molecular findings: Twenty-one CRCs were microsatellite stable (80.8%). KRAS mutations were identified in eight cases (30.8%). KRAS mutations were identified in codon 12 and 13 (11.5% each). None of the cases had BRAF V600E mutations. An NRAS mutation was identified in one patient (3.8%). Four cases were microsatellite instable-high (MSI-H) with no mutations identified in BRAF V600E (15.3%). These tumors were located in the rectum (n=2), left (n=1) and right (n=1) colon. One patient had an MSI-H tumor with no BRAF V600E mutation and a mutation in KRAS codon 13 (3.8%). One case did not have any tests (3.8%).

Histologic type: Twenty-three cases were diagnosed as

adenocarcinomas (88.5%), two cases as mucinous adenocarcinoma (7.7%), and one case was diagnosed as mixed adenocarcinoma with signet ring cells (3.8%). One of the 26 patients had a history of familial polyposis syndrome (3.8%). Three patients were diagnosed with Lynch syndrome after the colonoscopy findings (11.5%).

Discussion

This study identified the molecular and pathologic characteristics of the patients with YO-CRC at our institution. Our data shows two age groups with differing molecular profiles. Patients younger than 40 years old represented 46.1% of our patients with YO-CRC. Patients aged 40 years or less were more likely females that had CRCs measuring 5 to 10 centimeters, mucinous adenocarcinoma, microsatellite instability, absence of BRAF V600E mutations, presence of KRAS mutations in codon 13, hereditary cancer syndromes as familial adenomatous polyposis and Lynch syndrome, and distant metastases than patients age 40 to 50. These results are consistent with previous studies and suggest unique tumor behavior for younger age cohorts within the group of YO-CRC [2,3,7]. Approximately 80% of YO-CRCs are microsatellite stable and 20% are associated with familial syndromes [7]. Our findings are also in accordance with the national statistics [8]. In our study, 80.8% of the patients had microsatellite-stable tumors with no mutations in BRAF V600E, KRAS, or NRAS and approximately 15% were associated with familial syndromes.

The survival rate of CRC patients with MSS is 15% lower as compared with that of CRC patients with MSI-CRCs [8]. In our study, YO-CRC accounted for 15.2% of the CRCs diagnosed at our institution. This percentage is slightly higher than the percentage of cases identified in the USA [1]. One of the reasons may be the predominant population of B/N-HL and O/HL patients in our study. Another important finding of our retrospective study is the predominant location of these tumors in the rectum, which has important implications for prognosis and screening. According to the literature, increases in YO-CRCs in recent years have been mainly due to increases in rectal cancer, especially in whites [1,5]. Most of our patients with rectal CRCs were B/N-HL and W/N-HL. Patients with rectal carcinomas have worse survival than those with non-rectal colonic adenocarcinomas in stage IIIB but equal or better survival in stage IIC and stage IV [9,10]. In our study, seven of the 14 rectal tumors were diagnosed as stage IV (50.0%).

The 2018 American Cancer Society's screening guidelines recommend initiation of screening for CRC at 45 years old instead of 50 years old in a person with an average risk [11]. This change was based on data showing an increased incidence of CRC in younger populations, specifically of rectal cancer [11]. Our study also confirms that YO-CRCs often present at advanced stages. In our study, ten patients (38.5%) were aged 45 to 49 years old, most of which were diagnosed at advanced stages (IV and IIIB). All

our patients with YO-CRC presented with either rectal bleeding, changes in bowel movements, abdominal pain, and less frequently with a palpable mass which prompted them to consult. Changes in the screening guidelines will increase the early detection of CRC in asymptomatic patients. However, lack of education about the importance of screening for CRC, and no or limited medical insurance coverage are factors that influence the outcome of these patients. Screening has been related to a 53% reduction in mortality of CRC from 1974 to 2000 (American Cancer Society, 2017).

In fact, the most recent 2018 ACS screening guidelines recommend initiation of screening for CRC at 45 years old instead of 50 years old in a person with average risk. This was based on data showing increased incidence of malignancy in younger populations, specifically of rectal cancer. Also, stool-based tests were included in the latest guidelines as alternative methods of screening. These include FIT testing or HSgFOBT yearly, and multitargeted stool DNA test every 3 years. Otherwise, screening with structural test can be done with colonoscopy every 10 years, or flexible sigmoidoscopy/CT colonography every 5 years (ACS 2018). Although one of the limitations of our study is the number of cases, we can confirm that there are clinical, pathological, and molecular differences in the CRCs identified in patients younger than 50 years of age, and the subgroup of patients aged 40 years or younger, and further investigations of these characteristics is warranted.

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Disclosure/Conflict of Interest

The authors certify that they have no conflicts of interest to report.

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