Editorial

The reality of early-onset colorectal cancer: highlighting the needs in a unique but emerging population

Jane E. Rogers[1], Benny Johnson[2]

[1]Pharmacy Clinical Programs, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Correspondence to: Benny Johnson, DO. The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA. Email: bjohnson6@mdanderson.org.

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With 2021 estimating 149,500 new cases and 52,980 deaths in the United States, colorectal cancer (CRC) continues to be the third leading cause of cancer and the second leading cause of cancer death for both genders (1). CRC traditionally is a malignancy seen in older age [median age of diagnosis =66 years old] (2). However, the past decade shows a shift toward a younger population as the median age in the early 2000s was 72 years old. Although most patients will be older age, the previous decades show a decline in CRC (~30%) in the traditional population (≥65 years old) while incidence rates have risen in those <50 years old. Surveillance and epidemiology reports show a clear rise and continued expected rise in early-onset adult CRC (EOCRC), defined as those patients diagnosed at 18–49 years old (3,4). Bailey *et al.* evaluated CRC incidences during 1975–2010 which revealed a rise in estimated new CRC cases in patients <50 years old (3). The authors reported that by 2030, it is estimated the incidence rates for colon and rectal cancer are expected to increase by 90% and 124.2%, respectively for patients 20–34 years old; and 27.7% and 46%, respectively for patients 35–49 years old. Siegel *et al.* examined incidence patterns from 1974–2013 and concluded that individuals born circa 1990 compared to those born circa 1950 have double the risk of colon cancer and quadruple the risk of rectal cancer (4). Siegel *et al.* recently showed that since 1994, both genders have seen incidence rates increase >50% (5). Continued exploration of birth cohort patterns can help continue to shed light on etiology and provide hypotheses regarding occurrence.

Unlike many cancers of the gastrointestinal tract, CRC can be a preventable malignancy and has robust screening guidelines and modalities in the United States for those of older age (6-8). However, adherence to screening guidelines by the public continues to limit success of these strategies. Given the recent incidence increases in EOCRC, The American Cancer Society in 2018 lowered the traditional starting age of screening for average risk patients [those without familial risk, family history, and certain chronic illness such as inflammatory bowel disease (IBD)] from 50 to 45 years old (6). Other national guidelines have recently followed suit in lowering the starting age to 45 years old (7,8) which now mitigates provider hesitancy in ordering screening for this age group due to reimbursement concerns. Time to adapt to these new guidelines will be needed to determine an impact and if clinicians and the public will be adherent in obtaining screening. Nationwide adoption of these new recommended guidelines would hope to impact the percentage of patients in this age group that present with advanced disease. Those 45–49 years of age represent 44% of the EOCRC population (9); therefore, adapting to these new recommendations ideally would help to prevent or diagnose in early stage in many EOCRC patients.

CRC is well known to derive from non-cancerous polyps formed 5–10 years prior to CRC adenocarcinoma is formed (10). Therefore, a significant impact in prevention maybe made with the reduction of 5 years in initiating screening as the development of these pre-cancerous polyps have started to form well before age 45. Unfortunately, those <45 years of age must rely on monitoring of symptoms in order to prevent or diagnosis this malignancy at an early time

point. At least patients may have more clear symptoms in this population (rectal bleeding; changes in bowel habits) as EOCRC patients tend to be diagnosed with left-sided tumors (44% rectal primary and 25% distal CRC) (9) which tend to have less vague symptoms than those with right-sided tumors (fatigue; abdominal pain; weight loss). The American Gastroenterological Association supports endoscopy for any symptomatic patients; therefore, primary care physicians should consider a low threshold for workup for rectal bleeding in those <45 years old (11).

Given that screening guidelines have only recently changed and lack traditional screening methods in those <45 years of age, EOCRC is often diagnosed in advanced disease (~70% of cases will have stage III or IV disease) (12,13). The advanced diagnosis is in part likely related to being diagnosed long after symptoms have occurred. The CRC Alliance reported survey results (n=1,195) of young adult living patients or survivors. The results revealed relevant findings and concerns, most notably that 63% of responders indicated waiting 3–12 months before visiting their doctor with 41% waiting at least six months after they initial had experienced symptoms. Reasons for this lag time could be related to lack of knowledge of worrisome symptoms, denial of symptoms, embarrassment, lack of healthcare access, family and work obligations, and poor family/social support. In addition to patient lag time to seek medical help, most patients reported being misdiagnosed given low index of physician suspension in this age group. Most common patients' symptoms were wrongfully attributed to hemorrhoids or IBD. Sixty-seven percent reported seeing at least two physicians before they were diagnosed (some seeing up to four physicians). Data indicate a total average time to diagnosis in these patients as ~7–10 months' time (217–271 days) from symptom onset to medical contact. Compared to those with average onset, Scott *et al.* reported a median time of rectal cancer symptom onset to diagnosis of 217 days in those <50 years old compared to 29.5 days in those >50 years old (14). Therefore, education is a clear first step to alert the public and front-line primary care community of the changing incidence of this malignancy, the new screening guidelines supported by USPSTF, a lower threshold for initiating workup of GI symptoms, and removing barriers to obtaining a clear and early diagnosis.

The etiology for EOCRC is likely multifactorial and many hypotheses have been proposed. Most cases (70–80%) occur sporadically and are not related to a familial risk (15). Therefore, other outlooks of why these patients are developing this malignancy are needed. Globally, EOCRC rise is unique in high income areas such as the United States, Australia, Canada, Germany, and the United Kingdom (16). Traditional risk factors include obesity, lack of physical activity, non-Mediterranean Western diet, and diet high in red and processed meats and low in fiber (17). Some of these traditional factors are likely contributing to the EOCRC rise as the rise in obesity seen in the United State is clear. The National Center for Health Statistics for adults ≥20 years old show >80% are overweight, obese, or severely obese. From 1999–2000 through 2017–2018, the US obesity rate increased from 30.5% to 42.4% and severely obese cases increased from 4.7% to 9.2% (18). Additionally, human environmental external (antibiotics) and internal exposures (gut microbiota) affecting the microbiome are under investigation (19). Life exposures to certain elements (Westernized diets, poor diet, red/processed meats, obesity, stress, antibiotics, synthetic dyes, monosodium glutamate, titanium dioxide, high-fructose corn syrup, smoking, alcohol, unhealthy cooking practices) could be contributing to EOCRC as well as the impact of early life exposures are being evaluated (mode of nutritional provision in infancy, mode of birth delivery, early age antibiotic use, maternal stress/nutrition/infection) for cause (17).

Current guidelines do not distinguish CRC treatment based on age (20). In 2014, Lieu *et al.* reported on outcomes based on certain factors (performance status, age, and metastatic site) in Aide et Recherche en Cancérologie Digestive (ARCAD) database (n=20,023; 24 first-line trials) demonstrated early-age onset mCRC was a poor prognostic factor in treatment naïve patients (21). The authors reported that compared to middle age patients, younger patients had an increased risk of death (19%) and progression (22%) with first-line treatment. You *et al.* reported on characteristics between EOCRC to late-onset CRC using the National Cancer Database (22). In this analysis, EOCRC patients had more advanced stage disease at diagnosis and more frequently exhibited poor clinicopathological features like mucinous or signet ring histology and more poorly differentiated tumors. Additionally, Jácome *et al.* showed a greater negative impact of certain biomarkers for EOCRC in patients with CRC liver metastectomy (23) Analyses such as these and the fact that traditional standard of care therapy was studied in an older population, practitioners often took the approach of providing more aggressive treatment strategies (front-line triplet chemotherapy; more metastatic surgical approaches; overtreatment via adjuvant therapy). Kneuertz *et al.*

conducted a nationwide study of US hospitals accredited by the American College of Surgeons Commission on Cancer to compare EOCRC (age 18–49) and later-onset (age 65–75) who underwent surgical resection and adjuvant therapy. The authors found that younger patients were more likely to receive systemic chemotherapy at all stages compared to later onset CRC patients with even 6% of stage I patients receiving adjuvant chemotherapy which is not standard of care for stage I. They concluded that young adults received significantly more adjuvant therapy with only minimal gain compared to older patients (24). Unfortunately, these more intensive treatment strategies have not led to clear benefits.

With whole genome sequencing, classifying malignancies molecularly has gained traction with the hope to provide more insight into personalized medicine approaches. CRC has been classified into consensus molecular subtypes (CMS) molecularly into four types (CMS1) microsatellite-instability (MSI) immune characterized by hypermutated, MSI-high, diffuse immune infiltrate, BRAF mutated, CpG island methylator phenotype positive (CIMP), and somatic copy number alterations (SCNA)-low (CMS2) canonical characterized by MSI-stable, chromosomal instability, CIMP negative, SCNA-high, WNT and MYC activation (CMS3) metabolic characterized by MSI-stable, CIMP-positive, SCNA-intermediate, mutations in KRAS, PIK3CA, PTEN, APC (CMS4) mesenchymal characterized by MSI-stable, CIMP-negative, SCNA-high, TGF-beta activation, stromal infiltration, angiogenesis (25). All with distinctions of incidence, molecular characteristics, and survival. A study performed at our center by Willauer *et al.* attempted to differentiate clinical and molecular features of EOCRC (26). The results showed that early-onset patients were more likely to have synchronous metastatic disease, MSI disease, distal colon or rectal tumors, and less likely to have BRAF V600 mutations compared to patients aged ≥50. Patients <40 were predominantly CMS1 or CMS2 while CMS3 and CMS4 were uncommon in their evaluation. Very young patients (<30) were less likely to have mutations in APC and more likely to have signet ring histology. EOCRC also appeared to affect a greater number of Hispanic patients <40. Only a very small number of early-onset patients with metastatic disease (28/634 or 4%) had a recognized hereditary syndrome or IBD in the MDACC molecular cohort. Cercek *et al.* conducted a review at Memorial Sloan Kettering Cancer Center. Clinical, histopathologic, and genomic characteristics were compared between EOCRC [two groups: (I) 35 years old; (II) 36–49 years old] and average-onset CRC (≥50 years old) (27). The authors excluded those with hereditary syndromes and IBD from all but the germline analysis. EOCRC had more left-sided tumors, rectal bleeding, and abdominal pain as presenting characteristics. When evaluating the MSS group, no differences were seen histopathologically. Treatment response and survival were similar amongst age cohorts in those with MSS advanced CRC. Jin *et al.* reported in a similar fashion on clinical and molecular characteristics on early-onset stage III colon cancer patients (28). Patients were pulled for review from the Adjuvant Colon Cancer Endpoint database. Sex, race, performance status, risk group, tumor sidedness, and T stage were similar to those ≥50 years old. EOCRC patients were more frequently MSI/deficient mismatch repair and less likely to have BRAFV600E. The authors concluded that tumor biology was a more important prognostic factor than age of onset. More analysis on those with sporadic microsatellite stable (MSS) EOCRC patients is needed to determine if molecular differences between EOCRC *vs.* late-onset CRC tumors exist. Continued efforts are needed to identify personalized therapeutic approaches in these patients.

EOCRC patients not only have to process the life altering news of a cancer diagnosis, treatment, and stage but they also need to overcome a variety of unique challenges faced in this age group. Providers must be aware of these challenges including issues with body image, sexual dysfunction, fertility preservation, financial barriers, lack of insurance, treatment adherence, educational/work pursuits, psychological/social support, anxiety, depression, child-rearing while undergoing therapy, and in some cases palliative and end-of-life care (29). For example, CRC treatment can cause deleterious effects to both men and women reproductive potential (30). Abdominal and/or pelvic radiation can damage the ovaries and testes which is unavoidable with rectal cancers with current treatment schema in early-stage disease. Chemotherapy can lead to premature ovarian failure and high infertility risk. Holowatyj *et al.* recently reported on the unmet needs specifically in CRC and proposed path forward regarding prioritizing sexual health (30). Additionally, there is a rise in CRC diagnosed during pregnancy in EOCRC due to the rise in EOCRC and current trends in delayed childbearing as we have reported the challenges present in these cases through our center's experience (31).

Given these unique challenges, we recommend a multidisciplinary care model for EOCRC patient management involving many key disciplines and are in the process of activating such a dedicated center at our

Table 1 Ancillary services for multidisciplinary care of EOCRC patients

Ancillary service	Rationale
Internal medicine	Patient may lack primary care physician care established due to low degree of health issues
Genetic counseling	Establish familial hereditary syndrome and needed follow-up and counseling
Nutrition	Nutritional challenges associated with CRC
Social work	Psychosocial needs given early age diagnosis may need assistance with work/school efforts and child-rearing
Fertility specialist	Fertility preservation prior to treatment
Gynecologist	For rectal cancer radiation patients for vaginal dilator
Social support/advocacy groups	Connect and gain emotional support with others going through the same process
Financial resource specialists	Patient may not be insured. High-cost medications and treatments
Psychology support	Psychosocial needs given early age diagnosis may need assistance with work/school efforts and child-rearing
Pharmacists	Medication in depth counseling, adherence monitoring, assistance with high-cost medications
Integrative medicine	Desire to take alternative medicine
Supportive care consults	Help with supporting the patient through treatment via pain management, appetite, insomnia, bowel management, etc.

EOCRC, early-onset adult colorectal cancer.

institution. Discipline and rationale outlined in *Table 1*. Mendelsohn *et al.* reported on their 2-year experience at Memorial Sloan Kettering Cancer Center of a dedicated program for young onset CRC (32). The goals of the program were to provide coordinated and systematic clinical care to comprehensively address the unique needs of these patients and to establish a research infrastructure to study the etiology. The authors identified some important points of this population that virtual setting interaction would be more well received than phone calls and extensive counseling. They found that nutrition, sexual health, and psychology/psychiatry referrals were found to be most useful. Timing of these services were identified as a challenge.

In summary, EOCRC is a unique patient population and unfortunately represents commonplace in oncology clinics worldwide. Providers must be aware of the unique challenges that young patients with cancer are burdened with. We believe vital steps for transformative management of these patients is to initiate a culture of dedicated centers that target these specific needs along with continued research pathways to investigate etiology, molecular and clinical distinctions, translational science, and trust such efforts represent the best path forward for designing novel clinical trials dedicated to EOCRC.

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References

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer Statistics, 2021. CA Cancer J Clin 2021;71:7-33.
2. American Cancer Society. Colorectal Cancer Facts & Figures 2020-2022. Atlanta: American Cancer Society, 2020.
3. Bailey CE, Hu CY, You YN, et al. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975-2010. JAMA Surg 2015;150:17-22.
4. Siegel RL, Fedewa SA, Anderson WF, et al. Colorectal Cancer Incidence Patterns in the United States, 1974-2013. J Natl Cancer Inst 2017.
5. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. CA Cancer J Clin 2020;70:145-64.
6. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin 2018;68:250-81.
7. NCCN, Colorectal Cancer Screening. Version 2. 2021.
8. US Preventive Services Task Force; Davidson KW, Barry MJ, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. JAMA 2021;325:1965-77.
9. Siegel R. The epidemiology of early-onset colorectal cancer: opportunities for action. 2020 NCCRT Annual Meeting
10. Shussman N, Wexner SD. Colorectal polyps and polyposis syndromes. Gastroenterol Rep (Oxf) 2014;2:1-15.
11. Gómez A, Salguero G, García H, et al. Detection mutations in the DNA mismatch repair genes of hMLH1 and hMSH2 genes in Colombian families with suspicion of hereditary non-polyposis colorectal carcinoma (Lynch syndrome). Biomedica 2005;25:315-24.
12. Yarden RI, Newcomer KL, Never Too Young Advisory Board, et al. Abstract 3347: Young onset colorectal cancer patients are diagnosed with advanced disease after multiple misdiagnoses. AACR Annual Meeting 2019; March 29-April 3, 2019; Atlanta, GA.
13. Colorectal Cancer Alliance. 2018 Young-Onset Colorectal Cancer Survey Report. Available online: https://www.ccalliance.org/about/never-too-young/survey/2018-young-onset-colorectal-cancer-survey-report
14. Scott RB, Rangel LE, Osler TM, et al. Rectal cancer in patients under the age of 50 years: the delayed diagnosis. Am J Surg 2016;211:1014-8.
15. Stoffel EM, Murphy CC. Epidemiology and Mechanisms of the Increasing Incidence of Colon and Rectal Cancers in Young Adults. Gastroenterology 2020;158:341-53.
16. Mauri G, Sartore-Bianchi A, Russo AG, et al. Early-onset colorectal cancer in young individuals. Mol Oncol 2019;13:109-31.
17. Hofseth LJ, Hebert JR, Chanda A, et al. Early-onset colorectal cancer: initial clues and current views. Nat Rev Gastroenterol Hepatol 2020;17:352-64.
18. Hales CM, Carroll MD, Fryar CD, et al. Prevalence of obesity and severe obesity among adults: United States, 2017–2018. NCHS Data Brief, no 360. Hyattsville, MD: National Center for Health Statistics. 2020.
19. Sánchez-Alcoholado L, Ramos-Molina B, Otero A, et al. The Role of the Gut Microbiome in Colorectal Cancer Development and Therapy Response. Cancers (Basel) 2020;12:1406.
20. NCCN. Colon Cancer Version 3. 2021.
21. 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;32:2975-84.
22. You YN, Xing Y, Feig BW, et al. Young-onset colorectal cancer: is it time to pay attention? Arch Intern Med 2012;172:287-9.
23. Jácome AA, Vreeland TJ, Johnson B, et al. The prognostic impact of RAS on overall survival following liver resection in early versus late-onset colorectal cancer patients. Br J Cancer 2021;124:797-804.
24. 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;150:402-9.
25. Eng C, Rogers JE. Current synthetic pharmacotherapy for treatment-resistant colorectal cancer: when urgent action is required. Expert Opin Pharmacother 2019;20:523-34.
26. Willauer AN, Liu Y, Pereira AAL, et al. Clinical and molecular characterization of early-onset colorectal cancer. Cancer 2019;125:2002-10.
27. Cercek A, Chatila WK, Yaeger R, et al. A Comprehensive Comparison of Early-Onset and Average-Onset Colorectal Cancers. J Natl Cancer Inst. 2021;113:1683-92.
28. Jin Z, Dixon JG, Fiskum JM, et al. Clinicopathological and Molecular Characteristics of Early-Onset Stage III Colon Adenocarcinoma: An Analysis of the ACCENT Database.

J Natl Cancer Inst 2021;113:1693-1704.
29. Rogers JE, Woodard TL, Dasari A, et al. Fertility discussions in young adult stage III colorectal cancer population: a single-center institution experience. Support Care Cancer 2021;29:7351-4.
30. Holowatyj AN, Eng C, Lewis MA. Incorporating Reproductive Health in the Clinical Management of Early-Onset Colorectal Cancer. JCO Oncol Pract 2021;OP2100525. doi: 10.1200/OP.21.00525.
31. Rogers JE, Woodard TL, Gonzalez GMN, et al. Colorectal cancer during pregnancy or postpartum: Case series and literature review. Obstet Med 2021. doi: 10.1177/1753495X211041228
32. Mendelsohn R, Palmaira RL, Lumish M, et al. A Coordinated Clinical Center for Young Onset Colorectal Cancer. Oncologist 2021;26:625-9.

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