Diagnosis and Management of Rectal Cancer in Patients Younger Than 50 Years: Rising Global Incidence and Unique Challenges

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ABSTRACT

The global incidence of colorectal adenocarcinoma is stable or decreasing overall; however, the incidence of colorectal cancer in patients aged <50 years is increasing. Although some of this increase is due to hereditary cancer syndromes, this is not the sole explanation. Patients with early-onset rectal cancer in particular have unique disease patterns and face distinct challenges in their treatment. Molecular patterns of disease in this patient cohort are noteworthy and often represent an opportunity to target these cancers more effectively. Recent and ongoing trials focusing on minimizing toxicities and necessary therapy modalities and maximizing response and patient outcome are of paramount importance in this patient population. Additional resources are needed for this patient population, including fertility counseling and preservation, financial guidance, genetic counseling, and psychosocial support.

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Colorectal cancer (CRC) remains the third most common cancer for both men and women in the United States. In 2022, an estimated 151,030 new cases of CRC will be diagnosed, with rectal cancer accounting for 44,850 of these cases.[1] Although the incidence of CRC has stabilized or is decreasing in several countries, including the United States, the incidence of early-onset CRC has notably been increasing. This patient subset requires additional research, because early-onset CRC differs in terms of presentation and characteristics, specifically histologic and molecular features. Notably, this patient population also faces unique challenges that may impact outcomes. It is vital to improve understanding of the disease in this growing, young population of patients, for which optimal outcomes may result in many additional years or decades of good quality of life.

Most early-onset CRC occurs in the distal colon and rectum (25% and 37%, respectively, vs 23% in the proximal colon in 2012–2016).[2] This review focuses specifically on early-onset rectal cancer [EORC] and explores (1) epidemiologic trends; (2) characteristics, including presentation, staging, and histologic and molecular features; (3) treatment, including recent and ongoing trials that will impact potential outcomes; and (4) unique challenges facing this patient population.

Epidemiology and Risk Factors

Similar to CRC as a whole, the incidence of rectal cancer in all ages has been decreasing since the 1980s; it has decreased from 18.4 cases per 100,000 persons in 1985 to 10.4 in 2018. However, the incidence of EORC (ie, rectal cancer in patients aged <50 years) has concurrently been increasing, from 1.8 cases per 100,000 persons in 1985 to 3.2 in 2018[3,4]; this trend has been evident in the NCI SEER data (Figure 1A–C). The American Cancer Society estimated that 11.0% of colon cancers and 14.7% of rectal cancers in 2020 were diagnosed in people aged <50 years.[5] Although CRC continues to occur most frequently in patients aged 65 to 74 years, modeling of annual incidence rates project that by 2030, 10.9% of colon cancers and 22.9% of rectal cancers will be diagnosed in adults

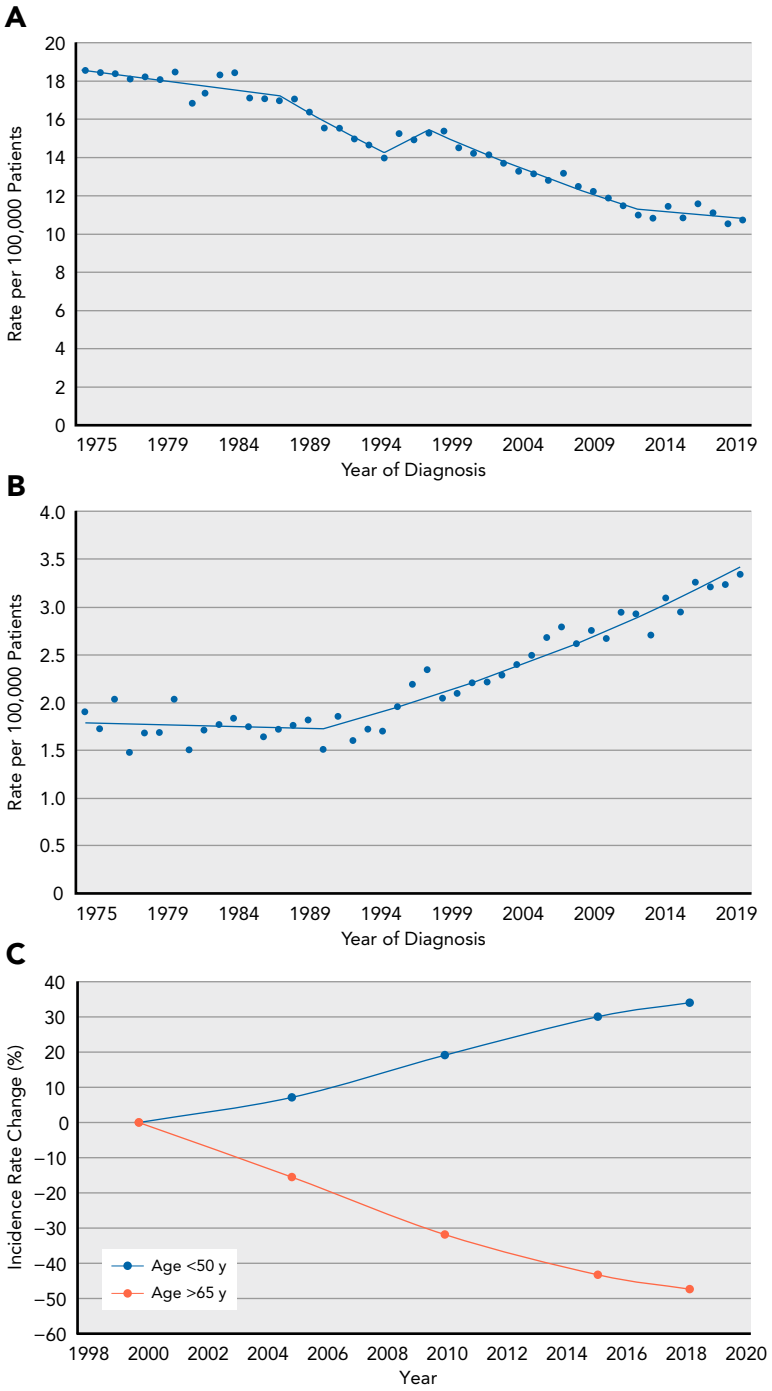

Figure 1. Incidence of early-onset rectal cancer in the United States. **(A)** Incidence of rectal cancer in all ages from 1975 to 2018 (SEER 9 sites), **(B)** incidence of rectal cancer in persons aged <50 years from 1975 to 2018, and **(C)** change in incidence rate for patients with rectal cancer aged <50 years versus >65 years from 2000–2018 (SEER 8 sites; created using https:/seer.cancer.gov/statistics-network/explorer).

aged <50 years. By 2030, age-period-cohort (APC)–based predicted incidence rates of rectal cancers are expected to increase by 124.2% for patients aged 20 to 34 years, while decreasing by 41% in patients aged >50 years.[6]

There are several risk factors for the development of EORC, including both inherited and environmental risk factors. In all ages, approximately 5% to 10% of CRC is hereditary, whereas in early-onset CRC, approximately 20% of patients have a pathogenic gene mutation.[7] Potential hereditary cancer susceptibility syndromes include Lynch syndrome (caused by germline mutations in mismatch repair [MMR] genes such as *MLH1*, *MSH2*,

MSH6, and *PMS2*) and polyposis syndromes, such as familial adenomatous polyposis (FAP; caused by mutations in *APC*) and *MUTYH*-associated polyposis (caused by biallelic mutations in *MUTYH* mutations).[8] Despite the increased prevalence of germline pathogenic mutations in this young population, it cannot solely account for the continued increase in incidence of EORC, raising questions regarding other potential risk factors. In patients with sporadic early-onset CRC, risk factors include (1) energy imbalance in the setting of metabolic syndrome, obesity, increased caloric intake, and low physical activity[9]; (2) changes to the gut microbiome, possibly due to fostering a proinflammatory environment[10,11]; and (3) exposures to substances such as to tobacco and alcohol (Figure 2).[7,8] Continued research into these potentially modifiable risk factors will be vital in determining future interventions that may slow or reverse current trends in incidence of EORC.

In May 2021, the United States Preventive Services Task Force (USPSTF) updated the guidelines for CRC screening, decreasing the recommended age for average-risk patients from 50 to 45 years. Previously, the ACS recommended initiating CRC screening at 45 years of age based on population disease burden, results of microsimulation modeling, and the expectation that screening will be similarly effective as in the older population.[12] Colorectal screening for the older population has enabled earlier diagnosis of disease, and is one of the factors that has contributed to the increased detection of and decreased mortality from CRC in patients aged ≥50 years.[13] At this time, the effect of this change in guidelines on incidence and mortality for adults aged <50 years is not yet clear, but the hope is that it will yield similar results.

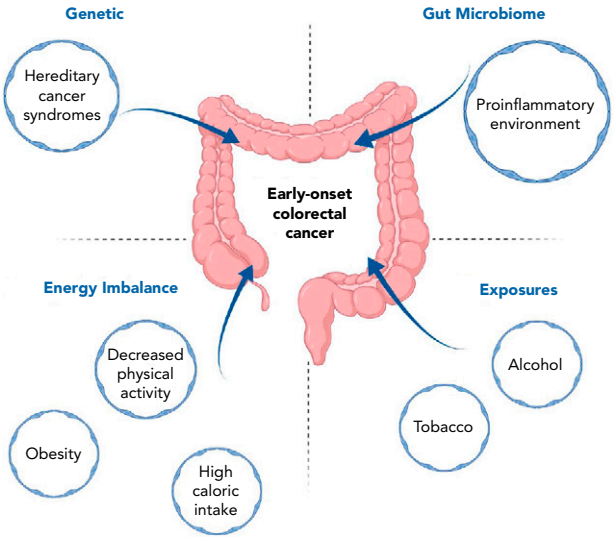

Figure 2. Selected risk factors for early-onset colorectal cancer.

Characteristics of EORC

CRC in younger patients is unique with regard to presentation, histology, and molecular characteristics. These patients typically present at more advanced stages (stage III–IV). According to SEER 21 data for rectal cancer diagnosed in 2010 through 2018, for the population aged <50 years in 2014, 21.9% had distant metastases and 31.3% had regional disease, whereas for the population aged ≥65 years, 16.4% had distant metastases and 27.3% had regional disease. This is likely because evaluation in younger patients is prompted by symptoms rather than screening. These symptoms are typically present for a longer duration prior to diagnostic evaluation than in patients aged >50 years, due to decreased awareness and lower clinical suspicion for cancer in young patients.[14,15] The recent change to the USPSTF guidelines may begin to bridge this difference.

Histologic characteristics have also been found to differ in patients with early-onset CRC. On histologic examination, studies have shown increased rates of poorly differentiated tumors, as well as increased rate of signet ring cell carcinomas.[16] This is pertinent, given that colorectal signet ring carcinoma has been shown to have worse outcomes, with SEER data showing a 5-year overall survival for all stages combined of only 25% compared with 64% in the total CRC population. One study found that in patients diagnosed at age ≤30 years, 37% of tumors were poorly differentiated versus 12% in the patients aged >50 years. In addition, 13% of cases in the younger group were signet ring cell carcinomas versus <1% in the older group.[16] Another study evaluating patients with CRC presenting prior to age 40 years identified signet ring cell histology in 13% of cases versus 1% in the group >40 years.[17]

In addition to germline pathogenic MMR mutations, studies have evaluated molecular mutation profiles in early-onset CRC, looking for potential differences in common somatic mutations.[18] These studies have thus far involved relatively small sample sizes but show some consistent findings. Specifically, these patients appear to have lower rates of *BRAF* V600E mutations, with incidence increasing by age.[19] Also of note is a lower incidence of *KRAS* mutations, as well as higher rates of *CTNNB1* mutations.[20] These studies evaluated CRC as a whole, as opposed to solely rectal cancers, and some differences in the molecular profiles may be related to the increased incidence of left-sided colon cancers in this young population.

Treatment of EORC

Metastatic Disease

Early-onset metastatic rectal cancer is often treated similarly to that of the general population. However, the prevalence of unique histologic and molecular features of this

subset of patients may impact potential treatment options. First-line treatment of metastatic disease is 5-FU–based cytotoxic chemotherapy regimens administered as doublet or triplet therapy, such as folinic acid/5-FU/oxaliplatin (FOLFOX), folinic acid/5-FU/irinotecan (FOLFIRI), capecitabine/oxaliplatin (CAPOX), or folinic acid/5-FU/oxaliplatin/irinotecan (FOLFIRINOX).[21] Addition of anti-VEGF therapy (ie, bevacizumab) to these regimens has also been shown to increase survival, as has addition of anti-EGFR therapy in patients with *RAS* wild-type disease.[22–27]

Treatment of metastatic disease has also been impacted by molecular testing and actionable biomarkers, which may allow for targeted therapy. These biomarkers include *RAS* mutations, *BRAF* V600E mutations, *HER2* amplification, microsatellite instability–high (MSI-H), and *NTRK* fusions.[7] For example, in previously treated patients with *BRAF* V600E mutations, the phase III BEACON trial showed longer overall survival (9 vs 5.4 months; $P<.001$) and higher objective response rates (26% vs 2%; $P<.001$) for combination therapy with encorafenib + cetuximab, compared with the control group receiving either cetuximab + irinotecan or cetuximab + FOLFIRI.[28]

The DESTINY-CRC01 trial evaluated trastuzumab deruxtecan in patients with HER2-positive disease (n=78) who had at least 2 prior lines of therapy, including those who had prior HER2-directed therapy, and found an objective response rate of 45.3% in cohort A.[29] The MOUNTAINEER trial also evaluated patients with HER2-positive disease who had prior lines of therapy (n=117) and found the overall response rate to tucatinib + trastuzumab was 38.1%, with a median duration of response of 12.4 months.[30] Both trials concluded that these agents provided promising activity in this subset of patients, with acceptable adverse-effect profiles. Because HER2 positivity is more prevalent in left-sided CRC, patients with EORC may be particularly affected and able to benefit from these HER2-directed therapies.

Because the rates of MSI are higher in patients with EORC, a greater proportion of patients can potentially be treated with frontline immune checkpoint blockade, based on the results from the KEYNOTE-177 study, which demonstrated efficacy of pembrolizumab monotherapy in patients with MSI-H/MMR-deficient (dMMR) disease.[31] In this pivotal study, patients treated with pembrolizumab had significantly longer median progression-free survival (16.5 vs 8.2 months; $P=.0002$) and higher response rates (43.8% vs 33.1%) compared with those receiving frontline chemotherapy. Overall survival was not improved with pembrolizumab, though this was likely impacted by the 60% crossover rate in the chemotherapy arm.

In addition, because patients with EORC have slightly lower rates of *RAS* and *BRAF* V600E mutations, there may be a larger number who can benefit from anti-EGFR therapy, because *RAS* mutations are a negative predictive biomarker of response to anti-EGFR therapy.[20]

Locally Advanced Disease

Patients with locally advanced rectal cancer (LARC) are treated similarly to the EORC population when compared with the general population, but there are a number of recent and ongoing trials that may have particular relevance for patients with EORC. Current guidelines recommend that patients with LARC receive trimodality therapy, with total neoadjuvant therapy (TNT) having recently become standard care when compared with the historical control of chemoradiotherapy (CRT) followed by total mesorectal excision (TME) and adjuvant chemotherapy. The Grupo Cancer de Recto 3 study was a randomized phase II trial that noted increased compliance and reduced toxicity with a TNT approach.[32] This has continued to be an area of investigation, with further studies evaluating details of the TNT approach, including differential sequencing of chemotherapy and CRT prior to TME.

One example of the TNT approach is the RAPIDO trial, which compared neoadjuvant CRT, TME, and adjuvant chemotherapy versus short-course radiation followed by neoadjuvant chemotherapy and TME. Results demonstrated that TNT was associated with a 7% lower disease-related treatment failure rate (23.9% vs 30.4%), 7% lower distant metastasis rate (20.0% vs 26.8%), doubled pathologic complete response (pCR) rate (28% vs 14%), and similar 3-year overall survival of 89% in both groups, and no unexpected toxicities or differences in surgery or postoperative complications.[33]

The OPRA trial evaluated the need for TME in patients with pCR following neoadjuvant therapy.[34] A total of 324 patients were enrolled and underwent TNT; if they achieved a clinical complete response (cCR), they were offered nonoperative management. Results thus far demonstrate that patients achieving a cCR could achieve organ preservation approximately 50% of the time. No difference in disease-free survival (DFS) has been observed between patients treated with nonoperative management and historical cohorts treated with CRT, TME, and adjuvant chemotherapy. It was also found that patients who received CRT followed by systemic therapy were more likely to preserve the rectum than those treated with systemic chemotherapy first. The order of neoadjuvant CRT and systemic chemotherapy did not otherwise affect survival or distant metastasis rates.[34]

Although the OPRA trial evaluated outcomes with omission of surgery in patients with a cCR, the phase II/III Alliance PROSPECT trial is evaluating the need for CRT in patients experiencing response to chemotherapy with FOLFOX (ClinicalTrials.gov identifier: NCT01515787). Patients are randomized to standard of care with TNT or to 6 cycles of neoadjuvant FOLFOX followed by restaging. Patients who experience a clinical response to chemotherapy (≥20% decrease in tumor burden)

proceed straight to surgery without CRT. Those who experience a poor response (estimated at <20% decrease in the tumor burden) undergo CRT prior to surgery. Results from PROSPECT are eagerly anticipated.

The UNICANCER-PRODIGE 23 trial evaluated escalation of neoadjuvant therapy with administration of FOLFIRINOX prior to CRT, TME, and then adjuvant chemotherapy. The primary endpoint was 3-year DFS. It enrolled 461 patients in France and compared this escalated regimen to standard of care consisting of CRT, TME, and adjuvant chemotherapy for 6 months. At a median follow-up of 46.5 months, 3-year DFS rates were 76% in the neoadjuvant chemotherapy group and 69% in the standard of care group, with a stratified hazard ratio of 0.69 (95% CI, 0.49–0.97; P=.034).[35]

There are also multiple recent and ongoing clinical trials focusing on patients with MSI-H/dMMR disease, which are quite relevant to the EORC population. The recently presented single-institution phase II trial at MSKCC (NCT04165772) is exploring PD-1 blockade alone as neoadjuvant therapy in patients with MSI-H rectal cancer, with the goal of evaluating whether this may allow patients to avoid subsequent radiation, chemotherapy, and surgery. Patients are treated with neoadjuvant dostarlimab for 6 months, with primary endpoints of overall response and complete response at 12 months after completion of PD-1 inhibitor treatment. Recent data from this trial indicate that all 12 patients who completed treatment have achieved an initial cCR with follow-up of at least 6 months. Further follow-up is required to determine durability of response.[36]

Similarly, the ongoing phase II EA2201 trial is evaluating neoadjuvant nivolumab + ipilimumab and short-course radiation in patients with MSI-H LARC (NCT04751370). In this study, patients with LARC receive nivolumab + ipilimumab for 2 cycles, followed by short-course radiation, then an additional 2 cycles of nivolumab + ipilimumab, followed by disease assessment and TME. The primary endpoint is pCR rate.

Results of these trials are providing important information for the treatment of all patients with LARC and will be particularly relevant to the patients with EORC for a number of reasons. For example, these are patients with an increased prevalence of Lynch syndrome and germline MMR mutations, and ongoing immunotherapy trials may allow these patients to avoid chemotherapy, radiation, and/or surgery. Additionally, with the goal of treatment in these patients being cure, we would anticipate they will live for many years following treatment. Therefore, studies that show noninferior or improved outcomes with decreased chemotherapy, radiation exposure, or surgery (allowing for organ preservation) will be particularly pertinent, because they may decrease treatment-related toxicities and long-term impact of treatment on quality of life. With regard to studies involving intensification of treatment, these younger patients may be more likely to have functional statuses which allow for such therapy, with the goal of improving outcomes.

Additional Challenges in EORC

With the continued increasing incidence of EORC, it is also vital to address the unique challenges this diagnosis presents to this patient population, including considerations of fertility preservation, the economic and financial ramifications of diagnosis and treatment, and the psychosocial stressors present in these young patients (Figure 3). The financial impact of CRC is well established, but patients with early-onset disease are particularly susceptible to the financial toxicity of cancer treatments.[37] These patients are more likely to be underinsured, and many may lack savings and assets, as well as employment security.[38] Many will often continue to work or return to work following treatment, which presents an additional stressor to these patients given the time toxicity of therapy.[39,40] Some may have families, including young children, who are

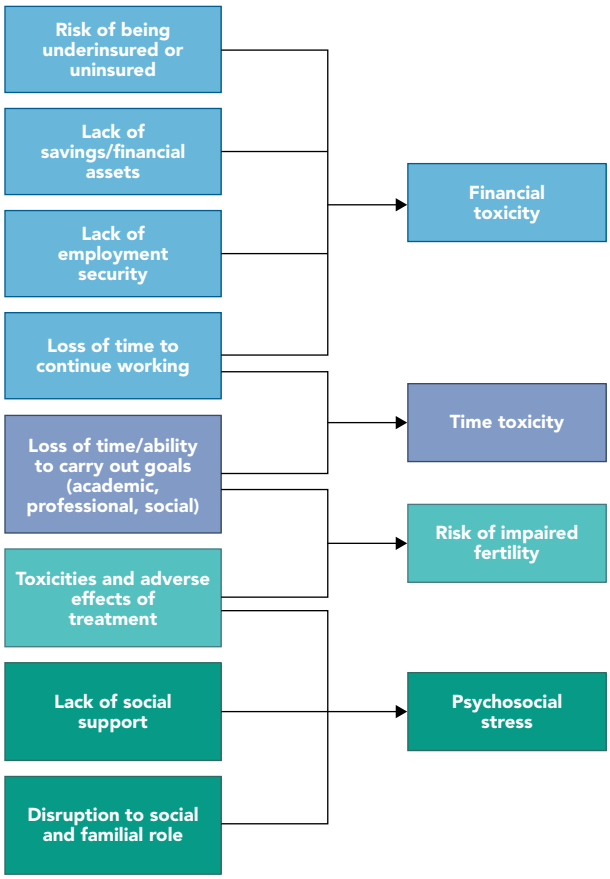

Figure 3. Challenges observed in patients with early-onset rectal cancer.

dependent on them for support. These factors should be taken into account at diagnosis, and require engagement of a multidisciplinary team to provide them with appropriate resources for peer support, educational and career counseling, financial guidance, reproductive health, genetic counseling, nutrition, psychosocial distress, spirituality, and physical and mental well-being.[41] There should be discussion of fertility preservation with these patients of childbearing age prior to initiation of cancer therapy.[42] Ongoing studies are evaluating reproductive health in patients aged <50 years following treatment of CRC.[7] It is also notable that these additional financial and psychosocial stressors are long-lasting for these patients, and continue to have effects for years following treatment.

Conclusions

EORC continues to increase in incidence in numerous countries, including the United States, even as the overall incidence of rectal cancer decreases.[1] Although some of these cases are secondary to hereditary cancer syndromes and germline mutations, the ultimate cause of this trend is currently unclear, although numerous associated risk factors have been identified. These patients are unique with respect to presentation, often presenting with disease at advanced stages, and differ in histologic features and molecular profiles, which may impact treatment options and responses. Recent USPSTF guideline changes decreasing the age of recommended screening from 50 to 45 years may help to mitigate the differences in presentation, allowing for earlier detection and diagnosis.

Currently, the treatment of patients with EORC is similar to those with late-onset disease. However, a number of recent and ongoing trials, particularly in the setting of locally advanced disease, hold significant potential ramifications for this patient population in improving complete response rates to neoadjuvant therapy, decreasing disease recurrence, and possibly allowing for decreased exposure to chemotherapy, radiation, and surgery, which could impact long-term survivorship in these patients, including treatment toxicities and quality of life. These patients face particular challenges regarding fertility, psychosocial, and financial stressors, which must be taken into account to optimize treatment outcomes. Ultimately, further research regarding treatment options and responses in patients with EORC is necessary to guide clinical decision-making and improve outcomes in this growing population of patients.

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References

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7–33.
2. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. CA Cancer J Clin 2020;70:145–164.
3. Islami F, Ward EM, Sung H, et al. Annual report to the nation on the status of cancer, part 1: national cancer statistics. J Natl Cancer Inst 2021;113:1648–1669.
4. Siegel RL, Torre LA, Soerjomataram I, et al. Global patterns and trends in colorectal cancer incidence in young adults. Gut 2019;68:2179–2185.
5. American Cancer Society. Colorectal Cancer Facts & Figures 2020-2022. Atlanta, Georgia: American Cancer Society; 2020.
6. 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.
7. Eng C, Jácome AA, Agarwal R, et al. A comprehensive framework for early-onset colorectal cancer research. Lancet Oncol 2022;23:e116–128.
8. Stoffel EM, Mangu PB, Gruber SB, et al. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology clinical practice guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology clinical practice guidelines. J Clin Oncol 2015;33:209–217.
9. Patel SG, Murphy CC, Lieu CH, et al. Early age onset colorectal cancer. Adv Cancer Res 2021;151:1–37.
10. Carvalho FA, Koren O, Goodrich JK, et al. Transient inability to manage proteobacteria promotes chronic gut inflammation in TLR5-deficient mice. Cell Host Microbe 2012;12:139–152.
11. Gronbach K, Flade I, Holst O, et al. Endotoxicity of lipopolysaccharide as a determinant of T-cell-mediated colitis induction in mice. Gastroenterology 2014;146:765–775.
12. Davidson KW, Barry MJ, Mangione CM, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA 2021;325:1965–1977.
13. Bénard F, Barkun AN, Martel M, et al. Systematic review of colorectal cancer screening guidelines for average-risk adults: summarizing the current global recommendations. World J Gastroenterol 2018;24:124–138.
14. Dharwadkar P, Greenan G, Singal AG, et al. Is colorectal cancer in patients younger than 50 years of age the same disease as in older patients? Clin Gastroenterol Hepatol 2021;19:192–194.e3.
15. Cercek A, Chatila WK, Yaeger R, et al. A comprehensive comparison of early-onset and average-onset colorectal cancers. J Natl Cancer Inst 2021;113:1683–1692.
16. 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;51:1812–1817.
17. Chang DT, Pai RK, Rybicki LA, et al. Clinicopathologic and molecular features of sporadic early-onset colorectal adenocarcinoma: an adenocarcinoma with frequent signet ring cell differentiation, rectal and sigmoid involvement, and adverse morphologic features. Mod Pathol 2012;25:1128–1139.
18. Holowatyj AN, Gigic B, Herpel E, et al. Distinct molecular phenotype of sporadic colorectal cancers among young patients based on multiomics analysis. Gastroenterology 2020;158:1155–1158.e2.

19. Willauer AN, Liu Y, Pereira AAL, et al. Clinical and molecular characterization of early-onset colorectal cancer. Cancer 2019;125:2002–2010.
20. Lieu CH, Golemis EA, Serebriiskii IG, et al. Comprehensive genomic landscapes in early and later onset colorectal cancer. Clin Cancer Res 2019;25:5852–5858.
21. Benson AB III, Venook AP, Al-Hawary MM, et al. NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer. Version 1.2022. Accessed April 10, 2022. To view the most recent version, visit https://www.NCCN.org
22. Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008;26:2013–2019.
23. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335–2342.
24. Cunningham D, Lang I, Marcuello E, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. Lancet Oncol 2013;14:1077–1085.
25. Van Cutsem E, Köhne CH, Láng I, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol 2011;29:2011–2019.
26. Bokemeyer C, Bondarenko I, Hartmann JT, et al. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. Ann Oncol 2011;22:1535–1546.
27. Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol 2010;28:4697–4705.
28. Kopetz S, Grothey A, Tabernero J. Encorafenib, binimetinib, and cetuximab in BRAF v600e–mutated colorectal cancer. Reply. N Engl J Med 2020;382:877–878.
29. Siena S, Di Bartolomeo M, Raghav K, et al. Trastuzumab deruxtecan (DS-8201) in patients with HER2-expressing metastatic colorectal cancer (DESTINY-CRC01): a multicentre, open-label, phase 2 trial. Lancet Oncol 2021;22:779–789.
30. Pelosci A. Tucatinib plus trastuzumab yields positive topline data in phase 2 MOUNTAINEER trial for HER2+ mCRC. Accessed on July 5, 2022. Available at https://www.cancernetwork.com/view/tucatinib-plus-trastuzumab-yields-positive-topline-data-in-phase-2-mountaineer-trial-for-her2-mcrc
31. André T, Shiu KK, Kim TW, et al. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. N Engl J Med 2020;383:2207–2218.
32. Fernández-Martos C, Pericay C, Aparicio J, et al. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo Cancer de Recto 3 study. J Clin Oncol 2010;28:859–865.
33. Bahadoer RR, Dijkstra EA, van Etten B, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:29–42.
34. Garcia-Aguilar J, Patil S, Gollub MJ, et al. Organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy. J Clin Oncol 2022;40:2546–2556.
35. Conroy T, Bosset JF, Etienne PL, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:702–715.
36. Cercek A, Lumish M, Sinopoli J, et al. PD-1 blockade in mismatch repair-deficient, locally advanced rectal cancer. N Engl J Med 2022;386:2363–2376.
37. Salsman JM, Bingen K, Barr RD, et al. Understanding, measuring, and addressing the financial impact of cancer on adolescents and young adults. Pediatr Blood Cancer 2019;66:e27660.
38. Lu AD, Zheng Z, Han X, et al. Medical financial hardship in survivors of adolescent and young adult cancer in the United States. J Natl Cancer Inst 2021;113:997–1004.
39. Daily K. The toxicity of time. J Clin Oncol 2018;36:300–301.
40. Fundytus A, Prasad V, Booth CM. Has the current oncology value paradigm forgotten patients' time?: too little of a good thing. JAMA Oncol 2021;7:1757–1758.
41. Akimoto N, Ugai T, Zhong R, et al. Rising incidence of early-onset colorectal cancer - a call to action. Nat Rev Clin Oncol 2021;18:230–243.
42. Stupart D, Win AK, Winship IM, et al. Fertility after young-onset colorectal cancer: a study of subjects with Lynch syndrome. Colorectal Dis 2015;17:787–793.