REVIEW ARTICLE

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Early-onset colorectal cancer: why it should be high on our list of differentials

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Abstract

Background: Early-onset colorectal cancer (EOCRC) (<50 years) incidence has increased in Australia and worldwide. However, the diagnosis of EOCRC is often delayed. Recent research has discovered some differences from later-onset colorectal cancer (LOCRC) (>50 years). An awareness of the unique features of EOCRC is crucial to reduce time from symptom onset to diagnosis.
Methods: A literature search was conducted on electronic databases (MEDLINE, EMBASE and Cochrane Library) using the search terms "early onset colorectal cancer" or "young onset colorectal cancer."
Results: The American Cancer Society has reduced the colorectal cancer screening initiation age to 45 for average-risk adults whilst screening programmes in the United Kingdom and Australia remain unchanged with initiation at 60 and 50, respectively. Exposures resulting in dysbiosis (obesity, westernised diet, alcohol, antibiotic and sugar-sweetened beverage consumption) have been linked with increased EOCRC risk. EOCRC is often left-sided presenting with rectal bleeding, altered bowel habit and constitutional symptoms. EOCRC is more commonly sporadic than hereditary, harbouring different genetic mutations than LOCRC. Comparative survival outcomes of EOCRC and LOCRC are conflicting with studies suggesting either better or poorer survival. Young patients better tolerate treatment-related toxicities, which may account for their improved survival despite comparatively advanced stages and poorer histopathological features at diagnosis.
Conclusion: Current EOCRC literature is limited by American-focused datasets and heterogenous EOCRC definitions and study designs (the greatest strength of evidence exists for EOCRC risk factor studies comprised of large retrospective cohorts). There is minimal research into the quality of life and surgical outcomes of EOCRC patients, and this area warrants further investigation.

Introduction

Early-onset colorectal cancer (EOCRC) is defined as the diagnosis of colorectal cancer (CRC) before the age of 50 and is increasing in incidence worldwide.[1] As a result, there has been a recent paradigm shift in CRC research to investigate EOCRC, with the current literature establishing differences to later onset colorectal cancer (LOCRC) (defined as a diagnosis of CRC over the age of 50) in terms of incidence, risk factors, clinical presentation, and pathological features and molecular profiles. EOCRC is typically diagnosed at later stages than LOCRC, which may be due to poor patient and clinician awareness or the attribution of symptomatology to more benign conditions common to younger populations. This study aims to review and summarize the current EOCRC literature to update Australian surgeons.

The incidence of EOCRC

Screening, surveillance, and treatment advances over recent years have decreased the general incidence and mortality rates of CRC in high-income countries. In contrast, the incidence of EOCRC has alarmingly increased in 19 (mainly European and Western) countries, with reports suggesting that EOCRC accounts for 11% and 10% of all male and female CRCs, respectively.[1,2] Whilst there are

minimal Australian studies investigating EOCRC incidence, a large portion of EOCRC incidence studies have used a cross-national comparative analytical approach where Australian data has been included. The results have demonstrated that, in Australia, the incidence of LOCRC decreased by 2.2% *per annum* whilst that of EOCRC increased by 2.8% *per annum* between 2006 and 2015.[1] Rising EOCRC incidence was proposed by Siegal *et al.*[3] to be a result of a birth cohort effect with their 2017 American study demonstrating that EOCRC rates and, more specifically, early-onset rectal cancer rates, increased from the 1980s and 1970s onwards in an age-dependent fashion, respectively. This birth cohort effect has been further demonstrated within an Australian cohort in a 2018 study by Faletto *et al.*[4] Comparatively, however, CRC and rectal cancer in Australians under the age of 50 increased from the mid-2000s and early 1990s onwards, respectively.

Changes to screening protocols

With a growing body of evidence demonstrating the increasing incidence of EOCRC and, in particular, Siegal *et al.*'s[1] demonstration of a strong American birth-cohort effect, the American Cancer Society updated their Colorectal Cancer Screening for Average-Risk Adults in 2018. The update included a qualified recommendation for adults aged 45 years or above to begin screening with either a high-sensitivity stool-based test or structural (visual) examination with all positive non-colonoscopy tests progressing to colonoscopy.[5] The United Kingdom's National Health Service (NHS) bowel cancer screening programme (BCSP) has not made any changes to their target range, recommending 2-yearly screening for those aged 60–74.[6] The Australian National Bowel Cancer Screening Program (NBCSP), implemented in a staged process, completed its full roll out in 2020 targeting those aged 50–74. Like NHS' BCSP, the target range for the Australian NBCSP remains unchanged, with a previous study demonstrating a less favourable benefits-to-harms ratio in extending screening to adults 45–49 years of age.[7]

Established risk factors for EOCRC

Age between 40 and 50 years, as opposed to <40 years, is one of the most significant non-modifiable contributing factors to EOCRC development.[2] Whilst being a male has been linked to EOCRC, being a female has been reported as a protective factor for colorectal adenomas.[2,8] Inflammatory bowel disease (IBD) is a well-established risk factor for CRC and has also been linked to EOCRC.[9] However, in a recent EOCRC study, it was a protective factor, with authors attributing this to intense surveillance protocols.[2] A family history of CRC is also a risk factor for EOCRC, however, the proportion of EOCRC patients with a family history of CRC in published EOCRC cohorts ranged from 11.1% to 25%, which suggests that the majority of EOCRC cases are sporadic.[2,9,10] Similar to other risk factors for LOCRC, studies have established cancer syndromes and race (specifically, black, pacific islander or Asian) as risk factors for EOCRC.[9,11] It is currently unclear as to what drives the ethnic disparities underlying EOCRC, but this may be related to lifestyle factors and socioeconomic status, which in itself has been documented as a risk factor for EOCRC primarily in American-only studies.

In comparison to non-modifiable risk factors, there is a greater predominance of EOCRC research to investigate modifiable risk factors that represent target areas for prevention with a heavy focus on the timing of the exposure. 'The Exposome' identifies exposures during development related to three domains (general external, specific external environment and internal environments).[12] In particular, exposures resulting in dysbiosis have been explored with weight gain and diet being the two exposures that have been the most heavily investigated. A recent 2021 systematic review and meta-analysis by Li *et al.*[13] found that overweight and obese younger adults have approximately 32% and 88% higher risk of developing CRC than those with average weight, respectively. Whilst previous literature has demonstrated sex-specific associations between EOCRC and young adulthood obesity,[14] this was not substantiated by Li *et al.*[10] A sedentary lifestyle has also been linked to EOCRC.[15] Westernized diet (i.e., increased fat and red meat and decreased fibre), which has also been referred to as a sulphur microbial diet, is an established risk factor for LOCRC and has been demonstrated by Rosato *et al.*[5] with the addition of increased consumption of alcohol (≥14 standards/week), to be linked with EOCRC.[5,12] Two 2021 studies have similarly reproduced these findings; a pooled analysis of 13 population-based comparative studies of EOCRC versus LOCRC which additionally demonstrated that a low-fibre (OR 1.19, 95% CI 1.08–1.31, $p < 0.001$) and low-folate diet (OR 1.16, 95% CI 1.08–1.26, $p < 0.001$) was linked more strongly with early-onset rectal cancer and an analysis of the Nurses' Health Study II data which found an association between those in the highest quartile of sulphur microbial diet scores and early-onset adenomas with greater malignant potential (villous/tubulovillous histology) (OR 1.65, 95% CI 1.12–2.45, $p = 0.04$).[7,16] Data from the Nurses' Health Study II has been further analysed by two studies which found that consumption of sugar-sweetened beverages both in adulthood and adolescence conferred a greater risk of EOCRC and colorectal adenomas.[17,18] More specifically, this risk was highest when consumption occurred during adolescence, with a linear relationship between the number of servings/day and a 32% increase in EOCRC risk.[17]

Chemical exposures resulting in dysbiosis have also been explored, albeit to a lesser extent. Whilst smoking has been previously associated with LOCRC, current evidence demonstrating its correlation with EOCRC is conflicting.[2,19,20] Aspirin (OR 0.66, 95% CI 1.68–2.91, $p < 0.05$) and non-steroidal anti-inflammatory drugs (OR 1.43, 95% CI 1.21–1.68, $p < 0.01$) have been found to be protective factors against the development of EOCRC in patients without IBD.[7,8] Certain antibiotics (quinolones and sulfonamides/trimethoprim) have been correlated with an increased risk of proximal EOCRC. However, the evidence behind this is low-level, comprising a singular abstract article.[21] A summary of modifiable and non-modifiable risk factors and protective factors are summarized in Table 1.

How does EOCRC present?

EOCRC typically involves either the left colon or rectum. Specifically, Siegal *et al.*[22] in their analysis of the North American Surveillance, Epidemiology and End Results (SEER) database, found

Table 1 Non-modifiable and modifiable risk factors and protective factors for EOCRC

Risk factors	Protective factors
Non-modifiable	
Male	Female
Age	IBD
Family history	
Cancer syndromes	
Race (non-Hispanic white, Hispanic, black, Asian)	
Modifiable	
Western diet/sulphur microbial diet	Aspirin
Alcohol	Non-steroidal anti-inflammatory drugs
Sugar-sweetened beverages	
Sedentary lifestyle	
Obesity	
Antibiotics (quinolones, sulfonamides/trimethoprim)	

that 41% and 35% of males and females diagnosed with EOCRC, respectively, had rectal cancer. This is significant as previous research has demonstrated a distinct difference in aetiology, biology and treatment response between proximal versus distal colonic cancers, with proximal cancers being associated with poorer prognostic features (lymph node involvement, lymphovascular invasion and advanced stage at diagnosis).[23] EOCRC presents with rectal bleeding, abdominal pain, constipation or diarrhoea, unintentional weight loss and iron-deficiency anaemia.[24] However, despite these red flag symptoms, studies have shown a significant delay in diagnosis of EOCRC compared to LOCRC. Chen *et al.*[25] found that it took a median of 128 days to diagnose EOCRC patients whilst it only took 79 days to diagnose LOCRC patients. Scott *et al.*[26] demonstrated an even greater disparity in delay from symptom onset to treatment commencement between early-onset and later-onset rectal cancer patients (217 versus 29.5 days, respectively). Previous literature has postulated that this diagnostic and treatment delay is due to a lack of patient awareness, insurance, and the attribution of symptoms to more common benign conditions by physicians and surgeons.[27] Despite these hypotheses, no statistically significant relationship between delayed diagnosis and late-stage EOCRC at presentation or adverse 5-year survival has been found.[25]

Pathological features and molecular profiles of EOCRC

EOCRCs display more aggressive pathological features in comparison to their LOCRC counterparts. Two large-scale comparative studies of the SEER (1334 patients aged 20–40 years versus 46 457 patients aged 60–80 years) and the North American National Cancer Database (64 068 patients <50 years versus 524 801 patients aged >50 years) demonstrated poorer differentiation and increased mucinous and signet-ring tumour morphology in their younger cohorts.[28,29] A smaller-scale single-institution study found higher proportions of locally advanced tumours invading adjacent structures (pT4) and lymph node metastases with an overall higher mean lymph node ratio in EOCRC versus LOCRC.[30] Moreover, Vuik *et al.*[31] established that within their EOCRC cohort exclusively, an inverse relationship existed between age and the presence of adverse pathological features; whereby being in a younger age group (20–29 versus 30–39 versus 40–49 years) was associated with an increased presence of signet-ring cells, poorly differentiated tumours, and lymph node involvement.

Studies comparing EOCRC and LOCRC have demonstrated that whilst gene mutation rates remain relatively the same, specific genes that have previously been established as prognostic biomarkers or treatment targets for LOCRC differ in EOCRC. EOCRCs harbour fewer KRAS, BRAFV600E and APC mutations but are more likely to have TP53 and CTNNB1 mutations.[32–34] EOCRC tumours are also more likely to undergo epigenetic changes (promoter methylation of the CpG islands).[27] In recent times, consensus molecular subtypes (CMS) have been used to classify CRC based on molecular features. Willauer *et al.*[34] found that younger patients were more likely to be of the CMS1 subtype characterized by high microsatellite instability and inflammatory/immunogenic markers, which is associated with germline mutations implicated in hereditary syndromes such as Lynch syndrome. Despite this, approximately 80–85% of EOCRCs are sporadic, microsatellite stable tumours.[35] Lam *et al.*[36] demonstrated a link between NR0B2 frameshift variants and increased susceptibility to microsatellite stable, APC-negative EOCRC. Further, recent molecular research has demonstrated a higher tumour mutational burden and distinct innate immune signature of EOCRC, has correlated specific gene mutations (SSA1, C7, CFD, CXCL3, IL1B, MET and TNS1), and aberrant pathways (wild-type WTN and mutated TGF-β pathway) with poorer overall survival (OS) in EOCRC and has identified accelerated ageing in normal mucosa of EOCRC patients as a potential contributor to carcinogenesis.[37–40] While molecular studies comprise a substantial amount of the current EOCRC body of literature, most of these studies are limited by a lack of reproducibility, heterogeneous inclusion criteria and methods, and small cohort sizes. To date, the molecular landscape and diagnostic, prognostic, and therapeutic biomarkers of EOCRC are relatively unknown.

Survival outcomes of EOCRC

At present, EOCRC survival studies are limited with varying EOCRC definitions and different survival measures. As such, the results of these studies are conflicting and are difficult to interpret without more uniform research. For example, two large studies found either superior or equivalent survival outcomes of EOCRC patients compared to their LOCRC counterparts despite a higher rate of advanced stage at diagnosis. More specifically, Saraste *et al.*[41] in their large Swedish study investigating 34 434 CRC patients found that EOCRC patients had a superior 5-year stage-adjusted disease-free survival (DFS) in comparison to those aged 50–74 and ≥ 75 (stage I: 0.96 versus 0.88 versus 0.69, $p < 0.001$; stage II: 0.90 versus 0.82 versus 0.62, $p < 0.001$ and stage III: 0.77 versus 0.68 versus 0.49, $p < 0.001$). O'Connel *et al.*[28] in their study of 47 791 SEER database patients demonstrated that whilst younger CRC patients (20–40 versus 60–80 years) had an overall worse 5-year cancer-specific survival (61.5% versus 64.9%, $p = 0.015$),

after adjusting for stage, the 5-year stage-specific survival was similar for stage I (93.3% versus 94.9%, $p > 0.05$) and III (58.9% versus 57.2%, $p > 0.05$) disease and better for stage II disease (88.6% versus 82.7%, $p = 0.01$). The improved survival benefit of EOCRC patients following stage adjustment was supported by Cheng *et al*.[42] Other studies investigating early-onset rectal cancer have found a significant improvement in OS at the 5- and 12-year marks.[43,44] The improved or equivalent survival outcomes of EOCRC patients in these studies has been attributed to their fewer comorbidities and higher receipt of neoadjuvant therapy and surgery. By contrast, a 2021 Australian rectal cancer study found that EOCRC patients had poorer median DFS post-neoadjuvant radiotherapy and surgery (4.67 versus 16.02 months, $p = 0.023$) as well as a poorer progression-free (2.66 versus 9.70 months, $p = 0.006$) and OS (40.46 versus 58.26 months, $p = 0.036$) following relapse. The authors of this study hypothesised that this was due to the more aggressive tumour biology of younger-onset rectal cancer and its potential to create a treatment-resistant environment.[45]

Limitations of current research

Although a substantive platform of EOCRC research exists, there are a few notable limitations. Firstly, most EOCRC studies comprise American-only cohorts, limiting the generalisability of their results. Secondly, aside from research into the risk factors of EOCRC, there is a substantially larger proportion of studies utilizing smaller cohort sizes and a retrospective study design. Hence, the impact of selection bias inherently associated with this study design cannot be ignored. Thirdly, there were heterogeneous definitions of EOCRC used within the literature with some studies defining EOCRC as diagnosis of CRC in patients <40 years and others using a cut-off of 50 years. Fourthly, comparison of variables and outcomes with LOCRC was only performed in roughly half of the studies limiting the ability to interpret comparative differences between these groups and thus ascertain whether current management guidelines translate (with the same efficacy) to EOCRC patients. Lastly, current literature primarily investigates the epidemiology, risk factors and molecular profile of EOCRC. However, studies focusing on health-related quality of life (HRQoL) and surgical outcomes are scarce.

Current gaps that require further exploration

To our knowledge, only one study exists which quantitatively investigates the HRQoL of EOCRC patients. Utilizing the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) questionnaire, Miller *et al*.[46] compared the HRQoL of EOCRC patients 6–18 months and 19–36 months from diagnosis. They demonstrated low global and domain-specific HRQoL scores overall and a significant positive correlation between time elapsed from diagnosis/relapse and physical (14.31 versus 16.56, $p = 0.001$) and emotional (11.3 versus 12.56, $p = 0.007$) well-being scores. Other current quality of life EOCRC research comprises small qualitative interview-style studies that lack reproducibility.[47] By comparison, HRQoL in CRC has been widely studied using a variety of measurement tools (FACT-C, the European Organization for Research and Treatment of Cancer Quality of life (EORTC) and Quality of Life Questionnaire Colorectal Cancer Module (QLQ-CR38/29)) with results demonstrating near equivocal HRQoL following primary treatment to the general population except for those patients receiving palliative care.[48] Despite this, scores were heterogeneous between measurements tools. To ascertain if this HRQoL disparity between EOCRC and general CRC is valid, further research comprised of large prospective studies comparing EOCRC and LOCRC utilizing a uniform HRQoL assessment tool is imperative.

Two recent American studies have investigated the comparative short-term surgical outcomes of EOCRC versus LOCRC and early-onset versus later-onset rectal cancer. In both studies, the early-onset groups had significantly reduced 30-day mortality (0.4% versus 1.8%, $p = 0.04$ and 0.3% versus 1.3%, $p = 0.04$, respectively) and 30-day postoperative complications (18% versus 22%, $p = 0.02$ and 25% versus 29%, $p = 0.02$, respectively) on univariate analyses, which did not demonstrate statistically significant differences on multivariate analyses. This was thought to be secondary to the confounding effect of the larger tumour sizes and aggressive histopathology of early-onset tumours.[49,50] Unfortunately, these studies were limited by their lack of long-term postoperative data and lack of information regarding surgical margins. Aside from these two studies, few other large non-American cohort studies investigate the surgical outcomes of EOCRC, and thus further research is warranted.

Conclusion

This review has demonstrated that EOCRC differs from LOCRC, characterized by subtle dissimilarities in risk factors (particularly regarding timing of exposure) and molecular profiles. Despite the increasing incidence of EOCRC and a plethora of studies that highlight the same, EOCRCs are still diagnosed at more advanced stages with a delay in diagnosis from symptom onset. Surgeon awareness of this is imperative to timely diagnosis and workup of EOCRC. Moreover, to optimize current treatment algorithms of EOCRC, larger, prospective research with an emphasis on survival, HRQoL and surgical outcomes needs to be performed.

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Conflict of interest

None declared.

Author contributions

Celine Garrett: Conceptualization; data curation; formal analysis; investigation; methodology; writing – original draft; writing – review and editing. **Daniel Steffens:** Conceptualization; data curation; methodology; project administration; resources; supervision; validation;

visualization; writing – review and editing. **Michael Solomon:** Conceptualization; data curation; methodology; project administration; resources; supervision; validation; visualization; writing – review and editing. **Cherry Ee Koh:** Conceptualization; data curation; methodology; project administration; resources; supervision; validation; visualization; writing – review and editing.

References

1. Siegel RL, Torre LA, Soerjomataram I *et al*. Global patterns and trends in colorectal cancer incidence in young adults. *Gut* 2019; **68**: 2179–85.
2. Agazzi S, Lenti MV, Klersy C *et al*. Incidence and risk factors for preneoplastic and neoplastic lesions of the colon and rectum in patients under 50 referred for colonoscopy. *Eur. J. Intern. Med.* 2021; **87**: 36–43.
3. Siegel RL, Fedewa SA, Anderson WF *et al*. Colorectal cancer incidence patterns in the United States, 1974-2013. *J. Natl. Cancer Inst.* 2017; **109**: djw322.
4. Feletto E, Yu XQ, Lew JB *et al*. Trends in colon and Rectal cancer incidence in Australia from 1982 to 2014: analysis of data on over 375, 000 cases. *Cancer Epidemiol. Biomarkers Prev.* 2019; **28**: 83–90.
5. Rosato V, Bosetti C, Levi F *et al*. Risk factors for young-onset colorectal cancer. *Cancer Causes Control* 2013; **24**: 335–41.
6. Public Health England. Bowel cancer screening: programme overview. Crown Copyright; 2015 [updated 17 March 2021; Cited 2 Nov 2021.] Available from URL: https://www.gov.uk/guidance/bowel-cancer-screening-programme-overview.
7. Archambault AN, Lin Y, Jeon J *et al*. Nongenetic determinants of risk for early-onset colorectal cancer. *JNCI Cancer Spectr.* 2021; **5**: pkab 029.
8. Low EE, Demb J, Liu L *et al*. Risk factors for early-onset colorectal cancer. *Gastroenterology* 2020; **159**: 492–501.e7.
9. Gausman V, Dornblaser D, Anand S *et al*. Risk factors associated with early-onset colorectal cancer. *Clin. Gastroenterol. Hepatol.* 2020; **18**: 2752–9.e2.
10. Stoffel EM, Koeppe E, Everett J *et al*. Germline genetic features of young individuals with colorectal cancer. *Gastroenterology* 2018; **154**: 897–905.e1.
11. Crosbie AB, Roche LM, Johnson LM, Pawlish KS, Paddock LE, Stroup AM. Trends in colorectal cancer incidence among younger adults-disparities by age, sex, race, ethnicity, and subsite. *Cancer Med.* 2018; **7**: 4077–86.
12. 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.
13. Li H, Boakye D, Chen X, Hoffmeister M, Brenner H. Association of Body Mass Index with Risk of early-onset colorectal cancer: systematic review and meta-analysis. *Am. J. Gastroenterol.* 2021; **00**: 1–11.
14. Liu PH, Wu K, Ng K *et al*. Association of obesity with Risk of early-onset colorectal cancer among women. *JAMA Oncol.* 2019; **5**: 37–44.
15. Nguyen LH, Liu PH, Zheng X *et al*. Sedentary behaviors, TV viewing time, and risk of young-onset colorectal cancer. *JNCI Cancer Spectr.* 2018; **2**: pky 073.
16. Nguyen LH, Cao Y, Hur J *et al*. The sulfur microbial diet is associated with increased risk of early-onset colorectal cancer precursors. *Gastroenterology* 2021; **161**: 1423–32.e4.
17. Hur J, Otegbeye E, Joh HK *et al*. Sugar-sweetened beverage intake in adulthood and adolescence and risk of early-onset colorectal cancer among women. *Gut* 2021; **0**: 1–7.
18. Joh HK, Lee DH, Hur J *et al*. Simple sugar and sugar-sweetened beverage intake during adolescence and risk of colorectal cancer precursors. *Gastroenterology* 2021; **161**: 128–42.e20.
19. Jung YS, Ryu S, Chang Y *et al*. Risk factors for colorectal neoplasia in persons aged 30 to 39 years and 40 to 49 years. *Gastrointest. Endosc.* 2015; **81**: 637–45.e7.
20. Kim JY, Jung YS, Park JH *et al*. Different risk factors for advanced colorectal neoplasm in young adults. *World J. Gastroenterol.* 2016; **22**: 3611–20.
21. Perrott S, McDowell R, Murchie P, Cardwell C, Samuel L. SO-25 global rise in early-onset colorectal cancer: an association with antibiotic consumption? *Ann. Oncol.* 2021; **32**: S213.
22. Siegel RL, Miller KD, Fedewa SA *et al*. Colorectal cancer statistics, 2017. *CA Cancer J. Clin.* 2017; **67**: 177–93.
23. Lim DR, Kuk JK, Kim T, Shin EJ. Comparison of oncological outcomes of right-sided colon cancer versus left-sided colon cancer after curative resection: which side is better outcome? *Medicine (Baltimore).* 2017; **96**: e8241.
24. Olivo R, Ratnayake S. Colorectal cancer in young patients: a retrospective cohort study in a single institution. *ANZ J. Surg.* 2019; **89**: 905–7.
25. Chen FW, Sundaram V, Chew TA, Ladabaum U. Advanced-stage colorectal cancer in persons younger than 50 years not associated with longer duration of symptoms or time to diagnosis. *Clin. Gastroenterol. Hepatol.* 2017; **15**: 728–37.e3.
26. Scott RB, Rangel LE, Osler TM, Hyman NH. Rectal cancer in patients under the age of 50 years: the delayed diagnosis. *Am. J. Surg.* 2016; **211**: 1014–8.
27. Burnett-Hartman AN, Lee JK, Demb J, Gupta S. An update on the epidemiology, molecular characterization, diagnosis, and screening strategies for early-onset colorectal cancer. *Gastroenterology* 2021; **160**: 1041–9.
28. O'Connell JB, Maggard MA, Liu JH, Etzioni DA, Livingston EH, Ko CY. Do young colon cancer patients have worse outcomes? *World J. Surg.* 2004; **28**: 558–62.
29. You YN, Xing Y, Feig BW, Chang GJ, Cormier JN. Young-onset colorectal cancer: is it time to pay attention? *Arch. Intern. Med.* 2012; **172**: 287–9.
30. Mueller M, Schneider MA, Deplazes B, Cabalzar-Wondberg D, Rickenbacher A, Turina M. Colorectal cancer of the young displays distinct features of aggressive tumor biology: a single-center cohort study. *World J. Gastrointest. Surg.* 2021; **13**: 164–75.
31. Vuik FE, Nieuwenburg SA, Nagtegaal ID, Kuipers EJ, Spaander MC. Clinicopathological characteristics of early onset colorectal cancer. *Aliment. Pharmacol. Ther.* 2021; **00**: 1–9.
32. Lieu CH, Golemis EA, Serebriiskii IG *et al*. Comprehensive genomic landscapes in early and later onset colorectal cancer. *Clin. Cancer Res.* 2019; **25**: 5852–8.
33. Serebriiskii IG, Connelly C, Frampton G *et al*. Comprehensive characterization of RAS mutations in colon and rectal cancers in old and young patients. *Nat. Commun.* 2019; **10**: 1–12.
34. Willauer AN, Liu Y, Pereira AAL *et al*. Clinical and molecular characterization of early-onset colorectal cancer. *Cancer* 2019; **125**: 2002–10.
35. Saizul Z, Siti-Azrin AH, Zakaria AD, Hassan A, Abdul Rahman WFW, Jalil NAC. BRAF V600E and mismatch repair proteins expression in sporadic young-onset colorectal cancer in Kelantan, Malaysia. *Oman Med. J.* 2021; **36**: e284.
36. Lam KK, Sethi R, Tan G *et al*. The orphan nuclear receptor NR0B2 could be a novel susceptibility locus associated with microsatellite-stable, APC mutation-negative early-onset colorectal carcinomas with metabolic manifestation. *Genes Chromosomes Cancer* 2021; **60**: 61–72.
37. Xu T, Zhang Y, Zhang J *et al*. Germline profiling and molecular characterization of early onset metastatic colorectal cancer. *Front. Oncol.* 2020; **10**: 568911.
38. Gardner IH, Siddharthan R, Watson K *et al*. A distinct innate immune signature of early onset colorectal cancer. *Immunohorizons* 2021; **5**: 489–99.

39. Singh MP, Rai S, Singh NK, Srivastava S. Transcriptomic landscape of early age onset of colorectal cancer identifies novel genes and pathways in Indian CRC patients. *Sci. Rep.* 2021; **11**: 1–11.
40. Joo JE, Clendenning M, Wong EM *et al*. DNA methylation signatures and the contribution of age-associated methylomic drift to carcinogenesis in early-onset colorectal cancer. *Cancers (Basel).* 2021; **13**: 2589.
41. Saraste D, Järås J, Martling A. Population-based analysis of outcomes with early-age colorectal cancer. *Br. J. Surg.* 2020; **107**: 301–9.
42. Cheng E, Blackburn HN, Ng K *et al*. Analysis of survival among adults with early-onset colorectal cancer in the National Cancer Database. *JAMA Netw. Open* 2021; **4**: e2112539.
43. Kolarich A, George TJ Jr, Hughes SJ *et al*. Rectal cancer patients younger than 50 years lack a survival benefit from NCCN guideline-directed treatment for stage II and III disease. *Cancer* 2018; **124**: 3510–9.
44. Zaborowski A, Murphy B, Creavin B *et al*. Clinicopathological features and oncological outcomes of patients with young-onset rectal cancer. *J. Br. Surg.* 2020; **107**: 606–12.
45. Habib R, Burgess NG, Bourke MJ *et al*. Outcomes of young patients diagnosed with locally advanced rectal cancer. *J. Gastrointest. Oncol.* 2021; **12**: 592–601.
46. Miller KA, Stal J, Gallagher P *et al*. Time from diagnosis and correlates of health-related quality of life among young adult colorectal cancer survivors. *Cancers (Basel).* 2021; **13**: 4045.
47. Blum-Barnett E, Madrid S, Burnett-Hartman A *et al*. Financial burden and quality of life among early-onset colorectal cancer survivors: a qualitative analysis. *Health Expect.* 2019; **22**: 1050–7.
48. Färkkilä N, Sintonen H, Saarto T *et al*. Health-related quality of life in colorectal cancer. *Colorectal Dis.* 2013; **15**: e215–22.
49. Ewongwo A, Hamidi M, Alattar Z *et al*. Contributing factors and short-term surgical outcomes of patients with early-onset rectal cancer. *Am. J. Surg.* 2020; **219**: 578–82.
50. Hanna K, Zeeshan M, Hamidi M *et al*. Colon cancer in the young: contributing factors and short-term surgical outcomes. *Int. J. Colorectal Dis.* 2019; **34**: 1879–85.