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ORIGINAL PAPER

# Treatment patterns and survival differ between early-onset and late-onset colorectal cancer patients: the patient outcomes to advance learning network

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## Abstract

**Purpose** Our objective was to describe differences in treatment patterns and survival between early-onset (< 50 years old) and late-onset colorectal cancer (CRC) patients in community-based health systems.

**Methods** We used tumor registry and electronic health record data to identify and characterize patients diagnosed with adenocarcinoma of the colon or rectum from 2010 to 2014 at six US health systems in the patient outcomes to advance learning (PORTAL) network. We used logistic regression to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) comparing the distribution of tumor characteristics and treatment patterns in early-onset versus late-onset CRC. Cox regression models were used to estimate adjusted hazard ratios (HRs) and CIs comparing survival between early- and late-onset CRC patients.

**Results** There were 1,424 early-onset and 10,810 late-onset CRC cases in our analyses. Compared to late-onset CRC, early-onset CRC was significantly associated with advanced-stage disease, high-grade histology, signet ring histology, and rectal or left colon location. After adjusting for differences in tumor and patient characteristics, early-onset patients were more likely than late-onset patients to have > 12 lymph nodes examined (OR 1.60, CI 1.37–1.87), to receive systemic therapy (chemotherapy or immunotherapy) within 6 months of diagnosis (OR 2.84, CI 2.40–3.37), and to have a reduced risk of CRC-specific death (HR 0.66, CI 0.56–0.79).

**Conclusions** Early-onset CRC is associated with aggressive tumor characteristics, distal location, and systemic therapy use. Despite some adverse risk factors, these patients tend to have better survival than older onset patients.

**Keywords** Colorectal cancer · Early-onset · Chemotherapy · Treatment · Survival

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## Introduction

Colorectal cancer (CRC) incidence and mortality have been declining in the United States, with CRC incidence in those who are of ages ≥ 50 years old decreasing by 32% and mortality falling by 34% from 2000 to 2013 [1, 2]. These declines have been largely attributed to increases in CRC screening uptake and advances in CRC treatment regimens [3–5]. In contrast to the CRC trends observed in those who are ages ≥ 50 years old, in Americans who are < 50 years old, CRC incidence is rising [2, 6]. This increase in early-onset CRC (CRC diagnosed at ages < 50 years old) has prompted new recommendations from the American Cancer Society to lower the age at which to start CRC screening for those at average risk from the current age of 50 years old down to 45 years old [7], although several other professional

organizations maintain a recommendation for initiating screening at age 50 [8–10].

The factors driving the increase in early-onset CRC are unknown, and it is unclear if different treatment protocols are needed for CRC patients diagnosed at early ages. Current National Comprehensive Cancer Network (NCCN) guidelines recommend the same treatment regimens for early- and late-onset CRC patients [11]. Despite these recommendations, prior studies have reported the use of more aggressive treatment regimens in early-onset than in late-onset CRC patients [12–14]. These prior studies have primarily been conducted using national databases. These databases may lack important information on patient characteristics, such as comorbidity status, and tumor characteristics that are important to account for in estimates of the association between aggressive treatment and early age at CRC diagnosis.

Also, the benefit of aggressive treatment in early-onset CRC patients is unproven [12, 13, 15]. Prior studies reported that early-onset CRC patients tend to be diagnosed with later stage tumors [14, 16–21]; this suggests that early-onset CRC tends to have a more aggressive CRC phenotype. Some early studies of survival in early-onset CRC also reported that patient survival is worse in early-onset CRC than in late-onset CRC [22–24], but these studies were small and failed to account for differences in tumor characteristics between early-onset and late-onset CRC patients. More recent studies suggest that stage-specific survival in early-onset CRC patients is similar or better than survival in late-onset patients [12, 14, 17–19].

Because most cancer patients receive their care in community-based settings, rather than in academic or National Cancer Institute-designated cancer centers [25], it is important to assess treatment patterns and survival among early-onset CRC patients receiving care in community-based settings. Thus, our objective was to gain a better understanding of the patterns of early-onset CRC treatment and survival across six large, diverse community-based healthcare systems in the United States.

## Methods

### Study population

This case–case comparison study was conducted within the Patient Outcomes To Advance Learning (PORTAL) network; PORTAL includes 10 integrated healthcare delivery systems that serve more than 11 million members nationwide [26]. Six of these healthcare systems participate in the PORTAL CRC Cohort, a retrospective cohort of healthcare system members who were ≥ 18 years old and diagnosed with adenocarcinoma of the colon or rectum from 1 January, 2010 through 31 December, 2014 [27]. The healthcare systems in the PORTAL CRC Cohort are as follows: HealthPartners in Minneapolis, MN (HPI), and five Kaiser Permanente systems, including Colorado (KPCO), Northwest in Portland, OR (KPNW), Northern California (KPNC), Southern California (KPSC), and Washington (KPWA, formerly known as Group Health). The study population for these analyses included PORTAL CRC Cohort members; we excluded CRC patients with in situ CRC, prior cancer, or previous colectomy. Study protocols and human subjects considerations were reviewed and approved by the Institutional Review Board (IRB) at KPCO, which is the IRB of record for the PORTAL CRC Cohort.

### Data sources and collection

The Virtual Data Warehouse (VDW) and the Patient-Centered Outcomes Research Institute Common Data Model (PCORI CDM; http://pcornet.org/pcornet-common-data-model/) were the sources of all study data; the VDW and the PCORI CDM use distributed common data models to collect and store standardized data elements derived from each healthcare system's administrative databases and electronic health records (EHR) [28, 29]. As part of the VDW, each healthcare system maintains a tumor registry that includes records of all cancer diagnoses for health plan members. These tumor registries employ North American Association of Central Cancer Registries (NAACCR) protocols to identify, confirm, and abstract common data elements for each cancer case, including cancer therapies administered within 6 months of diagnosis [30]. We used International Classification of Diseases, Oncology, Version 3 (ICD-O-3) codes to identify patients with CRC; these included C180, C182-C189, C199, and C209 (https://seer.cancer.gov/siterecode/icdo3_d01272003/) and histology codes to restrict to CRC patients with adenocarcinomas. Patient-level data from each healthcare system were pooled, cleaned, and harmonized at the PORTAL CRC Cohort Data Coordination Core in KPCO.

For each CRC patient, we collected information on age at diagnosis, date of diagnosis, health plan enrollment, gender, race/ethnicity, body mass index (BMI) (kg/m$^2$) for the period 12–24 months prior to diagnosis, and Charlson comorbidity score during the 24 months prior to diagnosis [31]. We also collected the following data from the tumor registry: stage according to the American Joint Commission on Cancer (AJCC), 7th edition, grade, anatomic site, histology, number of lymph nodes examined (≤ 12 or > 12), surgery, and receipt of systemic therapy (chemotherapy or immunotherapy) within 6 months of diagnosis. We also collected information on vital status, date of death, and cause of death. The date at which vital status was assessed ranged from 26 June, 2015 to 20 August, 2016, depending on each healthcare system's availability of these data.

### Statistical analyses

Data were pooled across health systems using a common data model. We used logistic regression to calculate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) comparing the distribution of tumor characteristics and treatment patterns in early-onset (< 50 years old) versus late-onset CRC (≥ 50 years old). Tumor characteristics included stage (polytomous model categorized as stage 1 (reference), 2, 3, or 4), anatomical site (polytomous model categorized as cecum (reference), right colon [transverse colon, hepatic flexure, ascending colon], left colon [sigmoid colon, descending colon, and splenic flexure], or rectum/rectosigmoid junction), summary grade (poorly differentiated/undifferentiated versus well/moderately differentiated), and summary histology (polytomous model categorized as non-mucinous adenocarcinoma (reference), mucinous adenocarcinoma, signet ring, other). Those with missing stage were dropped from the stage models (excluded $n = 318$ or 2.6%), and those with multiple tumor sites were dropped from the anatomical site models (excluded $n = 1$ or 0.01%). Treatment pattern outcomes included chemotherapy/immunotherapy, immunotherapy alone, and the number of nodes examined. The immunotherapy outcome models were restricted to stage 4 cases (included $n = 2{,}188$ or 18%), and the number of nodes examined outcome models were restricted to those with surgery and a known number of nodes examined (included $n = 10{,}343$ or 85%).

Cox proportional hazards regression models were used to calculate adjusted hazard ratios (HRs) and 95% CIs comparing the risk of death from all causes and CRC-specific death in early-onset vs late-onset CRC. For the CRC-specific death model, we censored those with missing cause of death data at the date of death ($n = 1{,}110$ or 9%).

Covariate adjustments in the tumor characteristics models included smoking status in the year prior to CRC diagnosis, health plan, race/ethnicity, gender, BMI, and Charlson comorbidity score. Additionally, we included anatomical site, stage, summary grade, and summary histology as adjustments to the treatment patterns models. Lastly, we additionally adjusted for chemotherapy/immunotherapy treatment and number of nodes examined in the overall and CRC-specific mortality models. Statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina).

### Exploratory analysis

For sensitivity analysis, we created three CRC onset age groups (18–49, 50–59, and 60+) for comparison in the tumor characteristics models. Exploratory analyses for all models incorporated an interaction between gender and CRC onset status. Finally, we estimated HRs and CIs for the time period ≤ 2 years after diagnosis and separately for the time period > 2 years following diagnosis and assessed whether the HRs differed between these time periods.

## Results

From 2010 to 2014, 16,199 patients with adenocarcinoma of the colon or rectum were diagnosed across the PORTAL CRC healthcare systems. Of these, we excluded 2,611 patient that had prior cancer, 1,346 with in situ CRC, and 8 with prior total colectomy. Thus, 12,234 patients were included in analyses; 1,424 of these were diagnosed at ages < 50 years old (early-onset CRC), and 10,810 were diagnosed at ages ≥ 50 years old (late-onset CRC). Compared to late-onset CRC patients, those with early-onset CRC were more likely to be Hispanic, never smokers, and to have Charlson comorbidity scores < 3. (Table 1)

### Tumor characteristics

Early-onset CRC patients were more likely than late-onset patients to be diagnosed at advanced stages (adjusted ORs for stage 2 vs. stage 1 = 1.48, CI 1.23–1.77; stage 3 vs. stage 1 = 2.23, CI 1.89–2.62; stage 4 vs. stage 1 = 2.85, CI 2.39–3.40). Early-onset CRC was also positively associated with left colon (adjusted OR for left colon vs. cecum = 2.24, CI: 1.82–2.76) and rectal anatomic locations (adjusted OR for rectum vs. cecum = 2.36, CI 1.92–2.91), high-grade tumors (adjusted OR for poorly differentiated/undifferentiated vs. well/moderately differentiated histology = 1.25, CI 1.07–1.46), and signet ring histology (adjusted OR for signet ring vs. non-mucinous adenocarcinoma = 1.70; CI 1.12–2.57) (Table 2). In analyses restricted to the most common histologic type, non-mucinous adenocarcinoma, the association between early-onset CRC and advanced stage remained unchanged (data not shown).

### Treatment

Overall, 83% of early-onset and 85% of late-onset patients received surgery. After adjusting for patient and tumor characteristics, there was no association between age at diagnosis and receipt of surgery for any stage (Table 3). Among those who underwent surgical resection, early-onset patients were more likely to have > 12 lymph nodes examined (adjusted OR 1.60, CI 1.37–1.87), even after accounting for differences in tumor and patient characteristics. Early-onset CRC patients were also more likely to receive systemic therapy within 6 months of diagnosis than late-onset patients (adjusted OR 2.84, CI 2.40–3.37). The association between increased systemic therapy use and early age at CRC onset was observed at every stage, including those with early-stage

**Table 1** Descriptive characteristics of the study population, by age at CRC diagnosis: PORTAL CRC patients diagnosed 2010–2014

| | Early-onset $n = 1,424$ | Late-onset $n = 10,810$ |
|---|---|---|
| | *n* (%) | *n* (%) |
| Race/ethnicity | | |
| Non-Hispanic White | 683 (48) | 6945 (64) |
| Non-Hispanic Black | 129 (9) | 994 (9) |
| Asian/Pacific Islander | 233 (16) | 1,192 (11) |
| Hispanic | 354 (25) | 1,504 (14) |
| Other/unknown | 25 (2) | 175 (2) |
| Sex | | |
| Male | 733 (51) | 5,456 (51) |
| Female | 691 (49) | 5,354 (50) |
| BMI (kg/m$^2$) | | |
| Normal | 428 (30) | 3,538 (33) |
| Overweight | 449 (32) | 3,707 (34) |
| Obese | 510 (36) | 3,271 (30) |
| Missing | 37 (3) | 294 (3) |
| Smoking status | | |
| Never | 934 (66) | 5,345 (49) |
| Former | 276 (19) | 3,981 (37) |
| Current | 162 (11) | 1,044 (10) |
| Missing | 52 (4) | 440 (4) |
| Charlson comorbidity score | | |
| 0 | 350 (25) | 1,728 (16) |
| 1 | 120 (8) | 937 (9) |
| 2 | 273 (19) | 1,812 (17) |
| 3+ | 266 (19) | 4,632 (43) |
| Missing | 415 (29) | 1,701 (16) |
| Healthcare system | | |
| HPI | 18 (1) | 122 (1) |
| KPCO | 72 (5) | 635 (6) |
| KPNC | 589 (41) | 4,405 (41) |
| KPNW | 65 (5) | 678 (6) |
| KPSC | 606 (43) | 4,234 (39) |
| KPWA | 74 (5) | 736 (7) |

Age distribution was as follows: ages < 40—3%, 40 to 44—3%, 45 to 49—6%, 50 to 59—22%, 60 to 69—26%, ≥ 70—40%

and those with late-stage disease. For stage 1 patients, 5% of late-onset patients received systemic therapy versus 12% of early-onset patients, and this difference remained statistically significant, even after adjusting for comorbidities, other patient factors, and tumor characteristics (OR 1.76, CI 1.15–2.70); for stage 2, systemic therapy was received by 25% of late-onset and 54% of early-onset patients (OR 2.63, CI 2.01–3.45); for stage 3, 75% of late-onset versus 95% of early-onset patients received systemic therapy (OR 3.79, CI 2.48–5.78) (Table 3). Among stage 4 CRC patients (the only patients typically eligible for immunotherapy during the study period), early-onset patients were also more likely to receive immunotherapy (OR 1.73, CI 1.13–2.66). (data not shown).

### Survival

Median follow-up time was 2.7 years for late-onset CRC patients and 2.5 years for early-onset patients. The risk of death from all causes, and from CRC, was lower in early-onset patients than in late-onset patients (HR for death from all causes = 0.66, CI 0.58–0.75; HR for CRC-specific death = 0.66, CI 0.56–0.79) (Table 4).

### Exploratory analyses

Results from the models with three age categories (18–49, 50–59, and 60+) were similar to the results for the primary analyses using dichotomous age categories (data not shown). None of the gender interactions or differences by stage in the treatment models were statistically significant (interaction *p*-values > 0.05). HRs comparing the risk of death in early- versus late-onset CRC did not differ significantly between the time period that included the first 2 years after diagnosis and the time period that was > 2 years after diagnosis (*p* value = 0.07).

## Discussion

In the community-based health systems within the PORTAL CRC network, we identified differences in treatment patterns and survival between early- and late-onset CRC patients. After accounting for differences in patient and tumor characteristics between early- and late-onset patients, early-onset CRC patients were more likely to have > 12 lymph nodes examined and more likely to receive systemic therapy than late-onset patients. We also found that although early-onset patients were more likely to present with aggressive tumor characteristics, for any given stage, histology, location, or tumor grade, early-onset CRC patients tended to have a better survival than late-onset patients.

NCCN guidelines do not recommend different treatment protocols for early-onset CRC [11], and prior studies have not proven a benefit for aggressive treatment in early-onset CRC patients [12, 13, 15]. Thus, it is unclear if factors, such as provider perception of increased benefit, better tolerance for systemic therapy in younger patients, or increased preference for systemic therapy among younger patients, are driving differences in treatment patterns between early- and late-onset patients. It is noteworthy that among stage 1 early-onset patients in our study population, 12% received systemic therapy, despite there being no recommendations for systemic therapy use in stage 1 CRC. Given that there are serious, long-term side effects associated with systemic

**Table 2** Odds ratios comparing tumor characteristics between early-onset and late-onset CRC patients in the PORTAL CRC Cohort 2010–2014

| | Early-onset *n* (%) | Late-onset *n* (%) | Adjusted OR (CI) |
|---|---|---|---|
| Stage | | | |
| 1 | 267 (19) | 3,194 (30) | Reference |
| 2 | 289 (21) | 2,731 (26) | 1.48 (1.23–1.77) |
| 3 | 486 (34) | 2,761 (26) | 2.23 (1.89–2.62) |
| 4 | 369 (26) | 1,819 (17) | 2.85 (2.39–3.40) |
| Anatomical site | | | |
| Cecum | 125 (9) | 1,918 (18) | Reference |
| Right | 209 (15) | 2,916 (27) | 1.07 (0.84–1.35) |
| Left | 535 (38) | 2,973 (28) | 2.24 (1.82–2.76) |
| Rectum | 531 (37) | 2,683 (25) | 2.36 (1.92–2.91) |
| Grade | | | |
| Well/moderately differentiated | 1,035 (73) | 7,987 (74) | Reference |
| Poorly differentiated/undifferentiated | 245 (17) | 1,696 (16) | 1.25 (1.07–1.46) |
| Histology | | | |
| Non-mucinous adenocarcinoma | 1,288 (90) | 9,612 (89) | Reference |
| Mucinous adenocarcinoma | 98 (7) | 811 (8) | 0.98 (0.78–1.23) |
| Signet ring | 30 (2) | 162 (2) | 1.70 (1.12–2.57) |
| Other/NOS | 8 (1) | 225 (2) | 0.44 (0.21–0.90) |

Adjusted for smoking status, health plan, race/ethnicity, sex (overall model), BMI (12–24 months prior to diagnosis), and Charlson comorbidity score

therapy for CRC [32, 33], the increased use of systemic therapy in early-onset CRC patients may result in higher rates of cancer treatment-related complications in this age group.

Prior studies that have evaluated differences in treatment patterns for CRC by age at onset have focused on disparities in guidelines-concordant care [34–36]. These studies have used national or state databases to evaluate the use of systemic therapy among CRC patients who are recommended to receive systemic therapy according to national guidelines. Consistent with our study results, these prior studies reported that older patients are less likely to receive chemotherapy [34, 35, 37] and have fewer lymph nodes examined than younger CRC patients [37]. These reports have resulted in a focus on improving guidelines-concordant care for older CRC patients to ensure that older CRC patients receive systemic therapy according to NCCN guidelines, and a study by Zhoa et al. reported improved guidelines-concordant care over time for older patients in Texas [36].

Other studies have raised concerns over not just disparities in chemotherapy use for older patients, but also inappropriately aggressive treatment in younger patients with CRC [12–14]. In a hospital-based study of over 13,000 early-onset CRC patients treated at US hospitals accredited by the American College of Surgeons Commission on Cancer, Knuertz, et al. reported increased use of systemic therapy, and particularly multi-agent regimens, in early-onset patients compared to older patients. Similar to our results, this study reported increased systemic therapy use in early-onset patients at all stages, with OR estimates comparing systemic therapy use in early-onset to late-onset CRC ranging from 2.74 (CI 2.44–3.07) in stage 4 patients to 3.93 (CI 3.58–4.31) in stage 2 patients [12]. Abdelsattar, et al. used Surveillance, Epidemiology, and End Results (SEER) cancer registry data for CRC patients diagnosed between 1998 and 2011, and found that among stage 4 CRC patients, early-onset patients were more likely to receive primary tumor resection and radiotherapy than late-onset patients [14]. Kolarich, et al. focused on evaluating rectal cancer treatment for more than 43,000 patients in the National Cancer Data Base who were diagnosed between 2004 and 2014 and reported that early-onset patients with stage 1 disease were more likely to receive radiation treatment outside of NCCN guidelines and that among early-onset stage II and III patients, neoadjuvant chemoradiation did not improve survival [13]. The results of these recent studies and our results shed light on the potential for overtreatment in early-onset CRC patients.

One limitation of prior studies is the inability to adjust for differences in comorbidity status between older and younger CRC patients. This may have introduced bias if increased comorbidity status at older ages is the primary driver of the observed differences in treatment patterns. Our study included high-quality data on both tumor and patient characteristics, including comorbidity status, allowing for estimates of the association between age at onset and systemic therapy use which take into account differences in comorbidity status. We also estimated associations between age at onset and CRC-specific survival which accounted

**Table 3** Odds ratios comparing initial treatment between early-onset and late-onset CRC patients in the PORTAL CRC Cohort 2010–2014, stratified by stage

| | Overall | | | Stage 1 | | | Stage 2 | | | Stage 3 | | | Stage 4 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Early N | Late N | OR (CI) | Early N | Late N | OR (CI) | Early N | Late N | OR (CI) | Early N | Late N | OR (CI) | Early N | Late N | OR (CI) |
| Surgery | | | | | | | | | | | | | | | |
| No | 238 | 1,633 | Reference | 7 | 127 | Reference | 14 | 121 | Reference | 23 | 126 | Reference | 187 | 1,009 | Reference |
| Yes | 1,186 | 9,177 | 1.13 (0.92–1.40) | 260 | 3,067 | 1.57 (0.71–3.44) | 275 | 2,610 | 1.01 (0.55–1.85) | 463 | 2,635 | 1.29 (0.79–2.09) | 182 | 810 | 1.01 (0.77–1.31) |
| Number of lymph nodes examined[a] | | | | | | | | | | | | | | | |
| ≤ 12 | 282 | 2,687 | Reference | 110 | 1,392 | Reference | 44 | 518 | Reference | 76 | 482 | Reference | 49 | 252 | Reference |
| > 12 | 899 | 6,474 | 1.60 (1.37–1.87) | 150 | 1,672 | 1.48 (1.13–1.94) | 229 | 2,090 | 1.69 (1.19–2.40) | 386 | 2,148 | 1.64 (1.24–2.15) | 131 | 554 | 1.57 (1.08–2.29) |
| Chemotherapy/immunotherapy | | | | | | | | | | | | | | | |
| No | 422 | 6,697 | Reference | 236 | 3,038 | Reference | 132 | 2,040 | Reference | 25 | 678 | Reference | 33 | 671 | Reference |
| Yes | 991 | 4,133 | 2.84 (2.40–3.37) | 31 | 156 | 1.76 (1.15–2.70) | 157 | 691 | 2.63 (2.01–3.45) | 461 | 2,083 | 3.79 (2.48–5.78) | 336 | 1,148 | 3.80 (2.58–5.60) |

Adjusted for smoking status, health plan, race/ethnicity, sex, BMI (12–24 months prior to diagnosis), Charlson comorbidity score, anatomical site, grade, and histology; overall model additionally adjusted for stage

[a]Lymph nodes examined analysis excluded those without surgery and those who were missing data on the number of nodes examined

**Table 4** Hazard ratios comparing the risk of death from all causes, and from CRC, between early-onset and late-onset CRC patients in the PORTAL CRC Cohort 2010–2014

| | Median years of follow-up | Death from all causes | | | CRC-specific death | | |
|---|---|---|---|---|---|---|---|
| | | *n* | Events (%) | HR (95% CI) | *n* | Events (%) | HR (95% CI) |
| Late-onset | 2.7 | 10,810 | 3,357 (31) | Ref | 9,803 | 1,826 (19) | Ref |
| Early-onset | 2.5 | 1,424 | 276 (19) | 0.66 (0.59–0.75) | 1,321 | 158 (12) | 0.66 (0.56–0.79) |

Adjusted for smoking status, health plan, race/ethnicity, sex, BMI, comorbidity, tumor site, tumor stage, grade, histology, chemotherapy/immunotherapy treatment, number of nodes examined

for differences in tumor characteristics, patient factors, and treatment patterns between early- and late-onset CRC; these robust analyses support prior studies suggesting that early-onset CRC patients tend to have better survival outcomes than late-onset CRC patients that have similar tumor characteristics [12–14, 17–19]. Given the overall consistency of results across multiple study populations supporting better survival in early-onset CRC patients, the use of aggressive treatment regimens for young CRC patients diagnosed with early-stage disease may be unwarranted and result in increased patient harms related to systemic therapy toxicity with little to no survival benefits to patients.

In addition to a well-characterized study data, the current study evaluated a large, diverse study population which allowed for precise estimates and adequate power to assess treatment patterns and survival in early-onset CRC. Another strength of our study is the use of a population-based cohort of CRC patients undergoing usual care in community-based settings; thus, our results are more generalizable than the results from clinical trials or from studies conducted in tertiary care, hospital-based settings. Despite these strengths, our study had several limitations. The study data captured the 1st course of treatment within 6 months of diagnosis; thus, we were unable to ascertain delayed treatment (> 6 months post-diagnosis) in both early- and late-onset CRC patients. Guidelines recommend treating early- and late-onset patients similarly, but in clinical practice, treatments administered (and their sequence) may vary by age and comorbidity. This may differentially influence, by age, the likelihood of receiving treatments beyond the 6-month tumor registry reporting window. We were also unable to assess specific treatment regimens or determine if treatment was stopped early. Also, we did not have data on prior colonoscopy use, treatment-related complications, or microsatellite instability status, so we were unable to assess these in our analyses.

In summary, our study highlights the increased likelihood of systemic therapy use for early-onset CRC patients treated in community-based settings. Given the increasing incidence of early-onset CRC in the United States, it is imperative to determine if there is overtreatment occurring in this age group. Because overtreatment in early-onset CRC patients may result in high numbers of CRC survivors needlessly impacted by long-term systemic therapy side effects, patient-, provider-, and system-level interventions to identify and reduce overtreatment should be tested, and if effective, implemented in community-based settings.

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## Compliance with ethical standards

**Conflicts of interest** The authors declare no potential conflicts of interest.

**Ethical approval** This study was conducted in accordance with the ethical standards of the institutional review board at Kaiser Permanente Colorado and with the 1964 Helsinki declaration and its later amendments.

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