Comparing Time to Diagnosis and Treatment Between Younger and Older Adults With Colorectal Cancer: A Population-Based Study

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BACKGROUND & AIMS: Younger adults (aged <50 years) with colorectal cancer (CRC) may have prolonged delays to diagnosis and treatment that are associated with adverse outcomes. We compared delay intervals by age for patients with CRC in a large population. METHODS: This was a population-based study of adults diagnosed with CRC in Ontario, Canada, from 2003 to 2018. We measured the time between presentation and diagnosis (diagnostic interval), diagnosis and treatment start (treatment interval), and the time from presentation to treatment (overall interval). We compared interval lengths between adults aged <50 years, 50 to 74 years, and 75 to 89 years using multivariable quantile regression. RESULTS: Included were 90,225 patients with CRC. Of these, 6853 patients (7.6%) were aged <50 years. Younger patients were more likely to be women, present emergently, have stage IV disease, and have rectal cancer compared with middle-aged patients. Factors associated with significantly longer overall intervals included female sex (8.7 days; 95% confidence interval [CI], 6.6–10.9 days) and rectal cancer compared with proximal colon cancer (9.8 days; 95% CI, 7.4–2.2 days). After adjustment, adults aged <50 years had significantly longer diagnostic intervals (4.3 days; 95% CI, 3.3–7.3 days) and significantly shorter treatment intervals (−4.5 days; 95% CI, −5.3 to −3.7 days) compared with middle-aged patients. However, there was no significant difference in the overall interval (−0.6 days; 95% CI, −4.3 to 3.2 days). In stratified models, younger adults with stage IV disease who presented emergently and patients aged >75 years had longer overall intervals. CONCLUSIONS: Younger adults present more often with stage IV CRC but have overall similar times from presentation to treatment as screening-eligible older adults.

Keywords: Colorectal Neoplasms; Young Adult; Time to Treatment; Delayed Diagnosis; Cohort Studies.

Although the incidence and mortality of colorectal cancer (CRC) among adults aged ≥50 years has decreased, in part due to population-based screening programs, younger adults (aged <50 years) have seen an increase in CRC incidence. Mortality rose an average of 1.1% each year from 2005 to 2017 in this population.1–6 Younger adults do not have access to population-based screening, and prolonged times to diagnosis and treatment may contribute to advanced disease at presentation and mortality for these patients.7–9

The literature reporting delay intervals in younger adults with CRC is heterogeneous and of variable quality. There is inconsistency in the definitions and magnitude of reported delay intervals, making it difficult to understand the typical diagnostic experience of these patients, and most studies have included <100 adults aged <50 years.9

A subset of the literature has attempted to compare interval lengths between younger and older adults, with mixed findings.10 Of 39 studies identified in a systematic review,10 14 (36%) found significantly longer intervals among younger adults. These comparisons were limited by small sample sizes, with a median number of only 87 younger adults, and 56% of studies did not present any adjusted analyses. The largest studies focused on the relatively short interval between diagnosis and treatment, and prediagnostic intervals were underrepresented.10 Although >170,000 adults aged <50 years were included in comparisons between the date of diagnosis and treatment, the largest study of prediagnostic intervals included only 4394 younger patients.11,12

As a result, less is known about the experiences of younger adults with CRC leading up to diagnosis. Compared with older adults, who have access to screening and in whom the diagnosis of CRC is not unexpected, those aged <50 years might be at risk of misdiagnosis or delayed diagnosis due to poor recognition of symptoms and access to care. Although a number of studies have compared interval lengths by age, this potential problem would be better studied within large, population-based studies that address the methodologic limitations of this literature, including adjustment for important confounders, appropriate statistical methods, and measurement of prediagnostic intervals.

Abbreviations used in this paper: ADG, Aggregated Diagnosis Group; CI, confidence interval; CRC, colorectal cancer; IBD, inflammatory bowel disease; IQR, interquartile range; OCR, Ontario Cancer Registry; ON-Marg, Ontario Marginalization Index.

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT
Younger adults (aged <50 years) with colorectal cancer may have prolonged delays to diagnosis and treatment that are associated with adverse outcomes.

NEW FINDINGS
This population-based cohort study, including 90,225 patients with colorectal cancer in Ontario between 2003 and 2018, found adults aged <50 years had longer times from presentation to diagnosis and shorter times from diagnosis to treatment initiation compared with adults aged 50 to 74 years. This resulted in an overall similar time from presentation to treatment between younger and older adults.

LIMITATIONS
We were not able to capture the time between onset of symptoms to presentation. Delay intervals were measured using algorithms based on health administrative and billing codes and were not validated against patient medical records directly.

IMPACT
Efforts focusing on postpresentation delays are unlikely to address differences in disease stage and outcomes among younger patients with colorectal cancer compared with older adults.

Our aim was to measure delay intervals extending from the date of first presentation to treatment start for CRC using comprehensive health administrative data in Ontario, Canada, and compare interval lengths between adults aged <50 years and older adults.

Materials and Methods

Study Design and Data Sources
This was a population-based retrospective cohort study of adults diagnosed with CRC in Ontario. Data were obtained from ICES (formerly known as the Institute for Clinical Evaluative Sciences), an independent, nonprofit research institute that maintains health administrative data for >14 million Ontario residents and provides deidentified linked data sets to its researchers. A unique encrypted identifier was used to link patient data from 15 separate data sources (Supplementary Material 1). We followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement in the preparation of this report (Supplementary Material 2). We also used the Aarhus checklist, a quality assessment tool designed specifically for cancer delay studies. The Aarhus statement and checklist is a consensus document published in 2012 that establishes standardized definitions for these time points and intervals and outlines common limitations of study designs in cancer delay research.

Ethics Approval
The Research Ethics Board at the University of Toronto (#41634) and St. Michael’s Hospital (#21-207) approved this study.

Study Context
Health care in Ontario is delivered by the province according to standards set by the federal government. Most health care is publically funded through a single-payer system, with notable gaps in coverage, including outpatient prescription drugs, long-term care, mental health care, dental care, and vision care. Access to specialist care, such as colonoscopy, generally requires a referral from family physicians or through emergency department-generated referrals.

Although the Canadian Task Force on Preventive Health Care has recommended annual or biennial fecal occult blood test for CRC screening in average-risk individuals since 2001, Ontario’s first population-based CRC screening program began in 2008. At-home stool-based tests are ordered by family physicians on the patient’s behalf, and samples are returned through prepaid envelopes. This program has been expanded to include letters mailed directly to eligible residents. Population-based data showed that 62.2% of eligible adults were up to date with CRC screening in 2016.

Patient Population
We identified Ontario residents aged 15 to 89 (inclusive) diagnosed with CRC between October 1, 2003, and December 31, 2018, using the Ontario Cancer Registry (OCR). The OCR is a high-quality population-based cancer registry operated by Cancer Care Ontario since 1964, with >94% of included CRCs being microscopically confirmed. Exclusion criteria included previous malignancy in the OCR, CRC diagnosis on death certificate only, appendiceal cancer, and inflammatory bowel disease (IBD). Patients with IBD were identified using a combination of diagnostic codes and the Ontario Crohn’s and Colitis Cohort, a population-based prevalence database capturing patients with IBD since April 1991 based on algorithms validated against medical record review. Administrative codes used in these definitions are presented in Supplementary Material 3.

Exposure
The exposure of interest was patient age, comparing younger and older adults with CRC. We divided the cohort into patients aged 15 to 49, 50 to 74, and 75 to 89 years. These cutoffs correspond to eligibility for CRC screening among average-risk individuals, as recommended by Cancer Care Ontario. In Ontario, regular screening is not recommended for adults aged <50 years without a first-degree family history of CRC. Routine screening is not generally recommended after age 74.

Outcomes
Using routinely collected health administrative data, we identified the date of the first presentation with CRC-related signs or symptoms, the diagnosis date, and the treatment start date. This enabled us to measure the diagnostic interval (presentation to diagnosis) and treatment interval (diagnosis to treatment start), as defined in the Aarhus statement. We also calculated the overall interval (presentation to treatment start).
Identifying Date of First Presentation, Diagnosis, and Treatment

We identified times along the pathway to treatment by using an algorithm based on administrative codes (including billing codes) adapted from prior work by Groome et al.\textsuperscript{15–23} for CRC, breast cancer, oral cancer, and pancreatic cancer. We previously reported our use of these methods to measure delay intervals among 6853 adults aged <50 years with CRC.\textsuperscript{20} We were able to successfully assign a date of first presentation and thus calculate the required delay intervals in >97% of younger adults.

In brief, the date of first presentation for each patient was identified by searching for the earliest encounter with the health care system for CRC-related signs, symptoms, or clinical care, to a maximum of 18 months before diagnosis. Eligible encounters were defined by groups of administrative and billing codes representing symptoms (eg, rectal bleeding), diagnostic tests (eg, cross-sectional imaging), diagnostic procedures (eg, endoscopy, endoscopic biopsy), and operations. Codes included in the algorithm are presented in Supplementary Material 3.

The date of diagnosis was determined from the OCR. The date of first treatment was defined as the first date of any chemotherapy administration, radiotherapy treatment, or surgical intervention after diagnosis.

Covariates

Age at diagnosis and sex were determined from the Registered Persons Database.\textsuperscript{29} Marginalization was measured using the Ontario Marginalization Index (ON-Marg), a validated tool that measures residential instability, material deprivation, dependency, and ethnic concentration at the neighborhood level.\textsuperscript{30} A summary score was created by averaging each individual’s quintile for the 4 measures, with higher scores indicating greater levels of marginalization.\textsuperscript{30} Canadian census data were used to assign individuals into income quintiles (1 being the least affluent and 5 being the most affluent), based on their postal code of residence.\textsuperscript{31} Rural patients were considered in a income separate category, because small populations make a determination of income unreliable using census data. Census data were also used to identify rural patients, defined as those living in communities of ≤10,000 individuals in size.

We used the Johns Hopkins Adjusted Clinical Group system to identify Major Aggregated Diagnosis Groups (ADGs), which represents groups of similar diagnoses in duration, severity, and etiology of the disease.\textsuperscript{32,33} Patients were classified as having 0, 1, or ≥2 Major ADGs. Patients with evidence of hereditary CRC syndromes (eg, hereditary nonpolyposis CRC) were identified by specialized Ontario Health Insurance Plan billing codes,\textsuperscript{35} and diagnostic codes occurring at any point from 10 years before the date of first presentation until the date of last contact (Supplementary Material 3).

Emergency presentations were defined as a first presentation occurring in the context of an emergency department visit or hospital admission or preceding hospitalization within 3 days. Administrative codes on the date of first presentation were used to categorize symptoms as anemia, gastrointestinal symptoms, or none/not determined. More detailed symptoms categories were also generated for descriptive purposes. The first type of imaging performed after the first date of presentation was used to divide initial imaging into cross-sectional (computed tomography or magnetic resonance imaging), non-cross-sectional (abdominal ultrasonography or x-ray), or no abdominal imaging. Imaging performed after diagnosis was not included in this definition.

Disease characteristics, including cancer site (rectal, sigmoid and rectosigmoid, and proximal colon), stage, and tumor histology, were obtained from the OCR. Histology was categorized as adenocarcinoma/no special type, mucinous adenocarcinoma, and other. Stage was available for patients diagnosed after 2007, using the American Joint Committee on Cancer classification.

Statistical Analysis

Patient characteristics were described for the cohort and according to age categories (age 15–49, 50–74, and 75–89 years). Continuous variables are presented as medians with interquartile ranges (IQR) or as means with standard deviations. Differences between age-groups were compared using Wilcoxon’s rank sum tests for continuous variables and χ² tests for categorical variables. Descriptive statistics and box plots are presented for the length of each delay interval in days according to increasing age and for interval lengths stratified by age and stage.

We used quantile regression to calculate the median difference between the 3 age-groups for the diagnostic interval, treatment interval, and overall interval. Quantile regression is a nonparametric approach that has been widely used in the cancer delay literature, because intervals are frequently right skewed and violate distributional assumptions with standard linear regression.\textsuperscript{24,35–39} Univariate and adjusted models were calculated. Multivariable models were adjusted for age, emergency presentations, rurality, the ON-Marg summary score, ADGs, sex, disease stage and site, and symptoms. Median differences with 95% confidence intervals (CIs) between age groups are presented. Additionally, stratified analyses were performed for each disease stage among patients who presented emergently and nonemergently. These models were adjusted for rurality, the ON-Marg summary score, ADGs, sex, disease site, and symptoms.

Sensitivity and subgroup analyses were performed. We repeated the analysis restricted to patients with nonemergency presentations. The adjusted comparison between younger and older adults was repeated, excluding patients with evidence of hereditary CRC syndromes. Missing data were handled using pairwise deletion.\textsuperscript{10} The analysis was performed using SAS 9.4 (SAS Institute Inc) and R (R Foundation for Statistical Computing) software. All statistical tests were 2-sided, and a P value of ≤.05 was considered statistically significant.

Results

Patient and Disease Characteristics

From the OCR, 95,990 patients aged 15 to 89 were diagnosed with CRC between 2003 and 2018. After exclusions, 91,385 patients remained. We were unable to assign a date of first presentation for 1160 patients (1.3%), resulting in 90,225 patients included in the analysis (Figure 1). Patient characteristics, stratified by age categories, are presented in Table 1. Of the total cohort, 6853 patients (7.6%)...
were aged <50, 52,144 (57.8%) were aged 50 to 74, and the remaining 31,228 patients (33.5%) were aged ≥75 years. There were important differences between the age-groups. Although 60% of patients aged 50 to 74 years were men, 52% of those aged <50 and 49% of those 75 to 89 years were men ($P < .001$). The oldest patients also had more comorbidities and were more likely to present with anemia compared with younger patients (Table 1). Additional information regarding symptoms is presented in [Supplementary Material 4](#). Patients aged <50 years with anemia were less likely to receive cross-sectional imaging as the initial imaging investigation compared with older patients (18% aged <50, 20% aged 50–74, and 26% aged ≥75 years). The most common codes used at presentation indicated nonspecific abdominal pain or gastrointestinal symptoms (59% of the cohort), followed by rectal bleeding (22% of the cohort).

Patients aged 75 to 89 years were most likely to present emergently (28%), followed by patients aged <50 years (23%), and middle-aged patients were least likely to present emergently (20%; $P < .001$). Younger adults were more likely to present with metastatic disease (20%) compared with those aged 50 to 74 (15%) and >75 years (14%; $P < .001$). These patients also presented more frequently with rectal cancer (31%) vs 25% of middle-aged patients, and 18% of patients aged >75 years ($P < .001$).

### Delay Intervals and Age

Descriptive statistics for the 3 intervals of interest are presented in Table 2. The median time from presentation to treatment (overall interval) was 124 days (IQR 63–236 days) for the cohort. Younger patients had significantly shorter overall intervals compared with older patients (median 109 days age <50, 121 days age 50–74, and 134 days age ≥75; $P < .001$). Interval lengths by age categories are visualized in Figure 2.

The overall interval can be divided into the diagnostic and treatment intervals. Most of this time was contained within the diagnostic interval (median, 89 days; IQR 32–202 days). Similar to the overall interval, patients aged <50 years had significantly shorter diagnostic intervals (Table 2). However, adults aged <35 years did have longer diagnostic intervals, with a median of 84 vs 77 days between first presentation and diagnosis for patients aged 35 to 49 years and 50 to 54 years (Figure 2). The treatment
interval was shortest in the youngest and oldest patients, with middle-aged patients having the longest times from diagnosis to treatment start (median, 23 days age <50; 27 days age 50–74, and 23 days age ≥75; \( P < 0.001 \)). The youngest patients (aged 15–34 years) had the shortest treatment intervals (median, 19 days) (Figure 2).
Table 2. Delay Intervals for a Cohort of Colorectal Cancer Patients in Ontario

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (N = 90,225)</th>
<th>Age &lt;50 (n = 6853)</th>
<th>Age 50–74 (n = 52,144)</th>
<th>Age ≥75 (n = 31,228)</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall interval, d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>124 (63–236)</td>
<td>109 (55–218)</td>
<td>121 (63–225)</td>
<td>134 (65–259)</td>
<td>&lt;.001</td>
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<tr>
<td>Mean (SD)</td>
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<td>148 (121)</td>
<td>157 (123)</td>
<td>170 (131)</td>
<td></td>
</tr>
<tr>
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<td>0–855</td>
<td>0–789</td>
<td></td>
</tr>
<tr>
<td>Missing, n</td>
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<td>384</td>
<td>4493</td>
<td>4982</td>
<td></td>
</tr>
<tr>
<td>Diagnostic interval, d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>89 (32–202)</td>
<td>78 (28–186)</td>
<td>85 (32–188)</td>
<td>99 (33–226)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>129 (121)</td>
<td>121 (117)</td>
<td>124 (117)</td>
<td>139 (126)</td>
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<tr>
<td>Range</td>
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<td>0–544</td>
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<tr>
<td>Missing, n</td>
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<td>384</td>
<td>4493</td>
<td>4982</td>
<td></td>
</tr>
<tr>
<td>Treatment interval, d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>25 (5–45)</td>
<td>23 (7–40)</td>
<td>27 (6–46)</td>
<td>23 (3–44)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>32 (36)</td>
<td>29 (31)</td>
<td>33 (36)</td>
<td>31 (37)</td>
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<tr>
<td>Range</td>
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<td>Missing, n</td>
<td>9859</td>
<td>384</td>
<td>4493</td>
<td>4982</td>
<td></td>
</tr>
</tbody>
</table>

SD, standard deviation.

<sup>a</sup>Kruskal-Wallis rank sum test; Pearson’s χ² test.

**Delay Intervals and Stage of Disease**

We explored interval lengths between age-groups by stage of disease, given the significant difference in the distribution of metastatic disease between younger and older patients (Figure 3). After stratification, patients aged <50 years continued to have shorter overall intervals within each stage compared with middle-aged and older patients. Among patients with stage I CRC, those aged <50 years had median overall intervals of 152 days compared with 155 days in those aged 50 to 74 years, and 164 days in those aged >75 years (Figure 3). A similar pattern was observed for the diagnostic interval and treatment interval, where patients aged <50 years had shorter or similar interval lengths compared with middle-aged and older patients.

Across all 3 intervals, patients with more advanced disease had shorter interval lengths compared with those with early disease (Figure 3).

**Association of Patient and Disease Factors With Interval Lengths**

Quantile regression was performed to assess the impact of patient and disease factors on the median length of each delay interval. Univariate results are presented in Supplementary Material 5, and adjusted models are summarized in Table 3. After multivariable adjustment, patients aged <50 years did not have significantly different overall intervals compared with those aged 50 to 74 years (−0.6 days; 95% CI, −4.3 to 3.2). However, when the diagnostic and treatment intervals were examined separately, younger adults had significantly longer diagnostic intervals (4.3 days; 95% CI, 1.3–7.3 days) and significantly shorter treatment intervals (−4.5 days; 95% CI, −5.3 to −3.7 days) compared with middle-aged patients. Patients aged >75 years had significantly longer overall intervals (6.9 days; 95% CI, 4.3–9.4 days) and diagnostic intervals (3.9 days; 95% CI, 2.0–5.9 days) compared with middle-aged patients, but there was no significant difference for the treatment interval. The effect sizes between age-groups after adjustment were small, with all significant median differences being <1 week.

Factors associated with significantly longer overall intervals included female sex (8.7 days; 95% CI, 6.6–10.9 days), rectal cancer compared with proximal colon cancer (9.8 days; 95% CI, 7.4–12.2 days), and ≥3 Major ADGs (84.1 days ≥3 Major ADGs vs 0; 95% CI, 79.1–89.0 days). After adjustment, emergency presentation (−65.6 days; 95% CI, −67.9 to −63.4 days) and more advanced stage (−48.6 days stage IV vs stage I; 95% CI −51.9 to −45.2 days) continued to be strongly associated with overall interval lengths (Table 3).

**Stratified Multivariable Quantile Regression**

In addition to multivariable quantile regression on the entire cohort, separate adjusted models were fit stratified by both emergency presentation vs nonemergency presentation and for each stage of disease. These models are shown in Figure 4, and the effect sizes are presented in Supplementary Material 6. In the stratified models, adults aged <50 years who presented emergently with stage IV disease had significantly longer overall intervals (8.1 days age <50 vs age 50–74; 95% CI, 0.6–15.7 days) and diagnostic intervals (5.0 days age <50 vs age 50–74; 95% CI, 2.3–7.7 days). The same comparisons were not significantly different for older patients. Younger adults also had longer diagnostic intervals among those with stage II disease. Otherwise, younger adults did not have significantly longer overall or diagnostic intervals compared with middle-aged patients across all other stratified models (Figure 4).

Younger adults had significantly shorter treatment intervals compared with adults aged 50 to 74 years with
nonemergent presentations (−5.4 days for stage I; 95% CI, −8.9 to −1.8 days) but not in patients with emergency presentations (−3.0 days for stage I; 95% CI, −11.6 to 5.5 days) (Figure 4). Stratified models were also explored for disease site and stage (Supplementary Material 7). There were no significant differences between adults aged <50 years and 50 to 74 years for the overall interval in these models.

Sensitivity and Subgroup Analyses
We performed additional sensitivity and subgroup analyses restricted to patients who did not present emergently, representing 69,269 patients with CRC from the overall cohort (Supplementary Material 8). Interval lengths were significantly longer in this subgroup, as described earlier. After adjustment, adults aged <50 years continued to have similar overall intervals compared with those aged 50 to 74 years (−4.3 days; 95% CI, −9.1 to 0.6), and there was no significant difference in the diagnostic interval in this subgroup analysis (1.9 days; 95% CI, −2.5 to 6.4 days).

Younger patients were more likely to have evidence of a hereditary CRC syndrome (8.7%, <50 years; 4.0%, 50–74 years; and 1.4%, ≥75 years; P < .001) (Table 1). Among adults aged <50 years, compared with patients who were not flagged, those with evidence of hereditary conditions were significantly less likely to present emergently (19% vs 24%; P = .007), have metastatic disease (5.6% vs 22%; P < .001), and have rectal tumors (26% vs 31%; P < .001). These results are presented in Supplementary Material 9. We repeated the multivariable model comparing interval lengths, excluding all patients flagged as having evidence of a hereditary CRC syndrome. This analysis reached the same conclusion as in the main cohort, with adults aged <50 years having significantly longer diagnostic intervals, shorter treatment intervals, and similar overall intervals compared with those aged 50 to 74 years (−0.6 days; 95% CI, −4.3 to 3.2 days) (Supplementary Material 9).
Discussion

This population-based study of 90,225 patients with CRC in Ontario, 6853 of whom were aged <50 years, found similar times from presentation to treatment among younger adults compared with middle-aged and older patients. Younger adults were more likely to have stage IV CRC and present emergently compared with those aged 50 to 74 years. Stage and presentation were also strongly associated with delay intervals, representing important confounders. After adjustment, younger adults had significantly longer diagnostic intervals (4.3 days; 95% CI, 1.3–7.3 days) and significantly shorter treatment intervals (–4.5 days; 95% CI, –5.3 to –3.7) compared with middle-aged patients, representing an overall similar total time from presentation to treatment. Young patients with stage IV disease experienced longer overall intervals than adults aged 50 to 74 years; however, the delay experienced was only an additional median 8.1 days.

Although studies comparing interval lengths between younger and older adults are heterogeneous, when significant differences are reported, they show shorter treatment intervals and longer prediagnostic intervals for younger adults. The largest study comparing treatment intervals by age is a National Cancer Database analysis by Gabriel et al, including >155,000 younger adults with CRC. In their unadjusted analysis comparing the treatment interval in those <50 years vs ≥60 years, the authors found a mean difference of –2.0 days (P < .001) for patients with colon cancer and –0.46 days (P < .001) for patients with rectal cancer.

Similarly, in a population-based United Kingdom study of 46,511 patients with CRC, Redaniel et al found adults...
Table 3. Multivariable Quantile Regression

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall interval</th>
<th></th>
<th>Diagnostic interval</th>
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<th>Treatment interval</th>
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<tbody>
<tr>
<td></td>
<td>Days (95% CI)</td>
<td>P value</td>
<td>Days (95% CI)</td>
<td>P value</td>
<td>Days (95% CI)</td>
<td>P value</td>
</tr>
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<td>Age category, y</td>
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<td>50–74</td>
<td>Days (95% CI)</td>
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<td>Days (95% CI)</td>
<td>P value</td>
<td>Days (95% CI)</td>
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<td>–4.5 (–5.3 to –3.7)</td>
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</tr>
<tr>
<td>75–89</td>
<td>6.9 (4.3 to 9.4)</td>
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<td>3.9 (2 to 5.9)</td>
<td>&lt;.001</td>
<td>0.3 (–0.3 to 0.9)</td>
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<tr>
<td></td>
<td>Days (95% CI)</td>
<td>P value</td>
<td>Days (95% CI)</td>
<td>P value</td>
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<td>–59.5 (–60.9 to –58.1)</td>
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<td>–7.9 (–8.5 to –7.2)</td>
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<tr>
<td>Yes</td>
<td>15 (12.7 to 17.3)</td>
<td>&lt;.001</td>
<td>40 (37.4 to 42.6)</td>
<td>&lt;.001</td>
<td>19.6 (19 to 20.2)</td>
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<td>Number of Major ADGs</td>
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<tr>
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<td>Days (95% CI)</td>
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<td>0</td>
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<td>&lt;.001</td>
<td>40 (37.4 to 42.6)</td>
<td>&lt;.001</td>
<td>19.6 (19 to 20.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2</td>
<td>35.6 (32.5 to 38.8)</td>
<td>&lt;.001</td>
<td>91.3 (87.3 to 95.2)</td>
<td>&lt;.001</td>
<td>–7 (–8.1 to –6)</td>
<td>.001</td>
</tr>
<tr>
<td>≥3</td>
<td>84.1 (79.1 to 89)</td>
<td>&lt;.001</td>
<td>91.3 (87.3 to 95.2)</td>
<td>&lt;.001</td>
<td>–7 (–8.1 to –6)</td>
<td>.001</td>
</tr>
<tr>
<td>ON-Marg Summary</td>
<td>Score (increase in 1 point)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>2.3 (0.9 to 3.7)</td>
<td>.001</td>
<td>2.5 (1.3 to 3.7)</td>
<td>&lt;.001</td>
<td>–0.3 (–0.7 to 0)</td>
<td>.051</td>
</tr>
<tr>
<td>Disease site</td>
<td>Proximal colon</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Days (95% CI)</td>
<td>P value</td>
<td>Days (95% CI)</td>
<td>P value</td>
<td>Days (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Sigmoid and rectosigmoid</td>
<td>0.5 (–2 to 3)</td>
<td>.689</td>
<td>–4 (–5.9 to –2.1)</td>
<td>&lt;.001</td>
<td>6.1 (5.5 to 6.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Rectum</td>
<td>9.8 (7.4 to 12.2)</td>
<td>&lt;.001</td>
<td>–6.1 (–8.3 to –3.9)</td>
<td>&lt;.001</td>
<td>19.6 (19 to 20.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Rurality</td>
<td>Urban</td>
<td></td>
<td>Rural</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Days (95% CI)</td>
<td>P value</td>
<td>Days (95% CI)</td>
<td>P value</td>
<td>Days (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Urban</td>
<td>0.1 (–2.9 to 3.2)</td>
<td>.928</td>
<td>0.1 (–2 to 2.3)</td>
<td>.913</td>
<td>1.3 (0.5 to 2.2)</td>
<td>.002</td>
</tr>
<tr>
<td>Rural</td>
<td>0.1 (–2.9 to 3.2)</td>
<td>.928</td>
<td>0.1 (–2 to 2.3)</td>
<td>.913</td>
<td>1.3 (0.5 to 2.2)</td>
<td>.002</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td></td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Days (95% CI)</td>
<td>P value</td>
<td>Days (95% CI)</td>
<td>P value</td>
<td>Days (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Male</td>
<td>8.7 (6.6 to 10.9)</td>
<td>&lt;.001</td>
<td>9.2 (7.5 to 10.9)</td>
<td>&lt;.001</td>
<td>–0.8 (–1.4 to –0.3)</td>
<td>.002</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Stage</td>
<td>I</td>
<td></td>
<td>II</td>
<td></td>
<td>III</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Days (95% CI)</td>
<td>P value</td>
<td>Days (95% CI)</td>
<td>P value</td>
<td>Days (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>I</td>
<td>–31.9 (–35 to –28.7)</td>
<td>&lt;.001</td>
<td>–23.1 (–25.9 to –20.3)</td>
<td>&lt;.001</td>
<td>–8.7 (–9.5 to –7.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>II</td>
<td>–31.1 (–34.4 to –27.9)</td>
<td>&lt;.001</td>
<td>–23.1 (–25.7 to –20.4)</td>
<td>&lt;.001</td>
<td>–9 (–9.8 to –8.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>III</td>
<td>–48.6 (–51.9 to –45.2)</td>
<td>&lt;.001</td>
<td>–37.1 (–39.5 to –34.7)</td>
<td>&lt;.001</td>
<td>–11.7 (–12.8 to –10.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>Gastrointestinal symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Days (95% CI)</td>
<td>P value</td>
<td>Days (95% CI)</td>
<td>P value</td>
<td>Days (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>None/not determined</td>
<td>–28.2 (–32.1 to –24.3)</td>
<td>&lt;.001</td>
<td>–33 (–36 to –29.9)</td>
<td>&lt;.001</td>
<td>9.1 (7.8 to 10.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>–10.5 (–13.9 to –7.1)</td>
<td>&lt;.001</td>
<td>–12.2 (–14.9 to –9.5)</td>
<td>&lt;.001</td>
<td>5.1 (4.2 to 6)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

NOTE. Effect estimates represent the median difference in days for interval length.

Aged 55 to 64 years experienced an additional 2.92 days (95% CI, 1.76–4.08) between diagnosis and treatment compared with those aged 15 to 44 years. Effect sizes appear consistently small for treatment interval comparisons. This is in line with our own findings, where younger adults experienced a median 23 days between diagnosis and treatment compared with a median 27 days for those aged 50 to 74 years (P < .001).

Similar to our findings, smaller studies have also shown longer diagnostic intervals for younger adults. However, none of these studies examined both the diagnostic and treatment intervals together, as we have, and some did not adjust for patient or disease characteristics. Our results suggest the small, significant effects in opposing directions for the diagnosis and treatment intervals by age result in similar overall times from presentation to treatment when younger adults are compared with middle-aged patients, after adjustment.

Existing studies that have attempted to compare the total time from presentation to treatment are small, with <800 total younger patients represented across 4 studies. Taken together, it appears longer times to diagnosis for younger adults may be compensated by faster subsequent treatment.

We found adults aged <50 years were more likely to present with metastatic CRC compared with older patients. Indeed, 1 in 5 younger patients presented with stage IV disease in our study. That younger patients present more
often with advanced disease is well recognized, and delays to diagnosis and treatment have been suggested to be contributory.\textsuperscript{7,8} The relationship between these factors is not straightforward. In a systematic review of 37 studies, including a meta-analysis of 17 studies, Ramos et al\textsuperscript{48} did not find a clear association between longer delay and CRC stage (pooled odds ratio, 0.98; 95% CI, 0.76–1.25). For all age groups studied, we found markedly shorter diagnostic intervals among patients with metastatic disease compared with early-stage disease. Similar findings have been observed in other cancer delay studies.\textsuperscript{24,26,49,50} Patients with more advanced disease likely experience noticeable or distressing symptoms, are necessarily unable to delay care, and are diagnosed quickly.\textsuperscript{51}

The strong relationships between CRC stage, interval length, and younger age highlights the importance of considering this factor in analysis, whether through adjustment or stratification. We used both approaches in our study. Because our results have failed to demonstrate differences in delays between younger and older adults that would be associated with meaningful disease progression, it appears unlikely that delay after presentation underlies the advanced disease stage of patients with CRC diagnosed when aged <50 years.

Our results suggest that current clinical practice in Ontario is triaging younger adults with CRC in a manner that results in similar times to treatment as older adults. Dedicated algorithms that consider young adults differently from older adults, or expedited referral programs that aim to decrease time to treatment, are unlikely to alter outcomes for younger adults with respect to stage or survival. However, our large-population based study can confirm clinicopathologic features noted by the existing literature for young-onset disease.\textsuperscript{52} CRC among adults aged <50 years

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{delay_forest_plot.pdf}
\caption{Forest plot demonstrates adjusted quantile regression models stratified by stage of disease and emergency vs nonemergency presentation. The adjusted median difference and 95% confidence interval between younger (aged <50 years) and older adults (aged ≥75 years) is shown compared with the reference group of adults aged 50 to 74 years (dashed line). (A) Overall interval: First presentation to treatment start. (B) Diagnostic interval: First presentation to diagnosis. (C) Treatment interval: Diagnosis to treatment start.}
\end{figure}
is less male-predominant compared with those aged ≥50
years. They are also less likely to present with anemia and
have particularly high rates of rectal tumors. Given the
concerning rise in the incidence of CRC in this population,
clinicians involved in the initial assessment of patients with
rectal bleeding and abdominal symptoms should be aware
of these trends. Younger age alone should not be the
determining factor in deciding to forgo investigation of
symptoms that could be consistent with CRC. There are also
opportunities to further increase awareness of the signs and
symptoms of CRC among younger adults.

Strengths of this analysis include the large sample size of
CRC patients and the population-based nature of the cohort.
This study reports the largest sample size of adults <50
years comparing prediagnostic intervals, an area that has
been underrepresented in the literature among high-quality,
population-based studies. To date, larger studies have
focused only on the relatively short treatment interval. We
used sophisticated algorithms based on administrative
codes and billing data to identify the date of first pre-
sentation. This methodology has been rigorously
developed for breast cancer, CRC, and oral cancer, and we
previously explored its application specific to younger
adults with CRC. The measurement and comparison of delay
intervals is complex—numerous analytic challenges have
been identified. We followed best practices and a checklist
for study quality from the Aarhus statement. Our interval
definitions are compatible with these consensus guidelines,
and we used quantile regression to compare interval
lengths, a distribution-free approach that acknowledges the
nonnormality of intervals. Finally, we accounted for emer-
gency presentations in both adjusted and stratified models.
This confounder has been identified as particularly impor-
tant for CRC, because it may help account for the different
speed of growth of tumors between patients.

This study has limitations. The algorithms used to
identify the date of first presentation are not validated
against patient medical records directly for CRC, although
this has been reported for oral cancer patients, and there is
the possibility for misclassification. Stage was available in
the OCR for patients diagnosed after 2007, so our models
including stage are restricted to those diagnosed after this
year. Our ability to identify hereditary CRC syndromes was
limited due to the lack of validated databases for these
conditions and because billing codes specifically for these
patients were only introduced in 2011.

We were necessarily limited to measuring intervals that
begin with some degree of interaction with the health care
system. Therefore, although we did not find evidence for
clinically meaningfully longer intervals among younger
patients, we were not able to capture time between onset of
symptoms and first presentation, the so-called patient inter-
val. In a study of 253 younger patients with rectal cancer in
a single institution, Chen et al. reported those aged <50 years
took a median 60 days to present after developing symptoms
compared with a median 30 days in those aged ≥50 years, a
difference that was statistically significant. It is possible, due
to poor access to care or lack of knowledge about alarm symp-
toms, that younger adults with CRC have prolonged patient
intervals that we are not able to capture using health admin-
istrative data. Finally, these comparisons may not be general-
zable to other jurisdictions, particularly those with different
uptake of CRC screening among older adults.

Conclusions
This large population-based study compared diagnostic,
treatment, and overall intervals between CRC patients aged
<50, 50 to 74, and ≥75 years. After accounting for impor-
tant confounders, including stage of disease and emergency
presentations, younger adults had statistically significantly
longer diagnostic intervals and shorter treatment intervals.
However, effect sizes were small, and the difference in the
overall time from presentation to treatment was not sig-
nificant. Further efforts focusing on delays after presenta-
tion are unlikely to address differences in disease stage and
outcomes compared with older adults.

Supplementary Material
Note: To access the supplementary material accompanying
this article, visit the online version of Gastroenterology at
www.gastrojournal.org, and at https://dx.doi.org/10.1053/
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