Original Investigation

Overtreatment of Young Adults With Colon Cancer
More Intense Treatments With Unmatched Survival Gains

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IMPORTANCE Colon cancer is increasing among adults younger than 50 years. However, the prognosis of young-onset colon cancer remains poorly defined given significant age-related demographic, disease, and treatment differences.

OBJECTIVE To define stage-specific treatments and prognosis of colon cancer diagnosed in young adults (ages 18-49 years) vs older adults (ages 65-75 years) outside of the clinical trial setting while accounting for real-world age-related variations in patient, tumor, and treatment factors.

DESIGN, SETTING, AND PARTICIPANTS A nationwide cohort study was conducted among US hospitals accredited by the American College of Surgeons Commission on Cancer. Participants were 13 102 patients diagnosed as having young-onset colon adenocarcinoma aged 18 to 49 years and 37 007 patients diagnosed as having later-onset colon adenocarcinoma aged 65 to 75 years treated between January 1, 2003, and December 31, 2005, and reported to the National Cancer Data Base.

EXPOSURES Patients who underwent surgical resection and postoperative systemic chemotherapy of curative intent.

MAIN OUTCOMES AND MEASURES The primary end point was stage-specific relative survival, an objective measure of survival among patients with cancer, adjusting for baseline mortality rates and independent of the data on cause of death. The secondary end point was stage-specific likelihood of receiving postoperative systemic chemotherapy.

RESULTS Most young-onset colon cancer was initially seen at advanced stages (61.8% had stage III or IV). After adjusting for patient-related and tumor-related factors, young patients were more likely to receive systemic chemotherapy, particularly multiagent regimens, at all stages relative to those with later-onset disease. These odds ratios were 2.88 (95% CI, 2.21-3.77) for stage I, 3.93 (95% CI, 3.58-4.31) for stage II, 2.42 (95% CI, 2.18-2.68) for stage III, and 2.74 (95% CI, 2.44-3.07) for stage IV. The significantly more intense treatments received by younger patients were unmatched by any survival gain, which was nil for stage II (relative risk, 0.90; 95% CI, 0.69-1.17) and marginal for stage III (relative risk, 0.89; 95% CI, 0.81-0.97) and stage IV (relative risk, 0.84; 95% CI, 0.79-0.90).

CONCLUSIONS AND RELEVANCE Young adults with colon cancer received significantly more postoperative systemic chemotherapy at all stages, but they experienced only minimal gain in adjusted survival compared with their older counterparts who received less treatment. This mismatch suggests that attention should be given to long-term cancer survivorship in young adults with colon cancer because they likely face survivorship needs that are distinct from those of their older counterparts.

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Significant progress has been made in treating colorectal cancer (CRC) over the past few decades. Among adults 50 years and older, the incidence of CRC has declined by 2% to 3% annually, and CRC survivors now comprise at least 10% of all cancer survivors in the United States.[1,2] In contrast, among adults younger than 50 years (the current recommended age at which to begin population-based screening), the incidence of CRC since 1975 has steadily increased.[3,4] Indeed, this persistent rise has been well documented in both population-based and hospital-based nationwide studies, observing annual percentage increases between 1992 and 2005 of 1.5% and between 1998 and 2007 of 2.1%.[3,4] Although it has been hypothesized that young-onset CRC harbors a distinctive biology, there is currently limited molecular understanding of this potentially unique disease entity.[5,6]

Surgeons are often the first referral physicians treating these young patients. However, at present, the prognosis of young-onset CRC is poorly defined,[6] making it difficult to advise about postoperative treatments and surveillance. The results of some studies[5,7,8] suggest poorer survival in the young, while other studies show comparable or better survival relative to patients diagnosed as having later-onset disease.[9-11] This heterogeneity may be due to several unadjusted factors, including age-related differences in the disease stage at presentation,[4,9] in the treatments received,[10] in the spectrum of the treatment modalities used,[10,12,13] and in age-related baseline mortality rates. Furthermore, as both surgical and adjuvant treatments have evolved over time, institutional experiences accumulated over long periods further contribute to the varied findings.[14] Last, data derived from the clinical trials setting may not reflect variations in real-life clinical practice.[15,16]

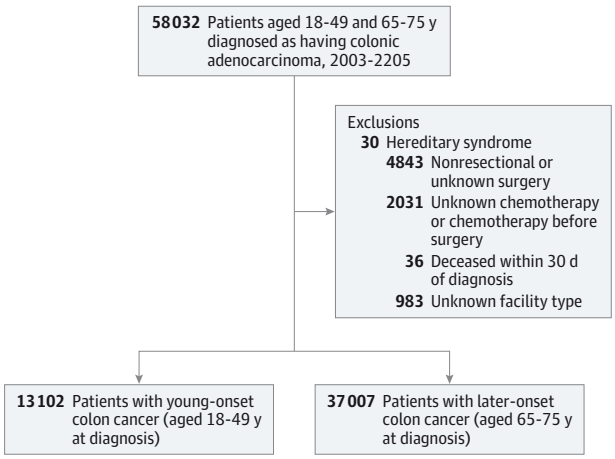
To overcome these difficulties, we conducted a nationwide comparative cohort study to examine the relative survival of young adults with colon cancer, adjusting for variations in patient and tumor factors, comorbidities, disease stage, stage-specific treatments received, and baseline mortality rates. Because both cancer treatments and disease prognosis affect the experience of cancer survival, we examined age-related differences in the types and intensity of chemotherapy treatments, as well as differences in the relative survival gains. Our findings highlight the potential for unique survivorship care needs among young adults with colon cancer.

Methods

Study Setting and Data Source

We used the National Cancer Data Base (NCDB), a hospital-based nationwide cancer registry that is a joint program of the American College of Surgeons Commission on Cancer and the American Cancer Society. The NCDB captures more than 70% of all cancer diagnoses annually within the United States from almost 1500 accredited hospitals. Trained site-based cancer registrars collected and submitted all data using standardized coding definitions outlined by the Commission on Cancer's Facility Oncology Registry Data Standards manual.[17] Data quality assessments are performed using a combination of electronic and site-specific methods.[18] All data were deidentified. The University of Texas MD Anderson Cancer Center Institutional Review Board granted this study an exempt waiver for patient consent.

Figure 1. Young Adults (Ages 18-49 Years at Diagnosis) vs Older Adults (Ages 65-75 Years at Diagnosis) With Colon Cancers



The patients were treated between January 1, 2003, and December 31, 2005, and were reported to the National Cancer Data Base.

Patient Populations and Study Variables

The NCDB was queried for patients diagnosed as having adenocarcinoma between January 1, 2003, and December 31, 2005. The *International Classification of Diseases for Oncology, Third Edition* (*ICD-O-3*) codes searched were histology codes 8140 to 8144, 8210 to 8211, 8260 to 8263, 8440, 8480 to 8481, and 8490 of the colon and topography codes C180, C182 to 189, and C199. This short time frame was chosen to minimize temporal bias and to reflect a period when treatments for colon cancer were consistent with current standards.[19,20] Patients with known hereditary syndrome (familial adenomatous polyposis *ICD-O-3* codes 8220-8221) were excluded. Also excluded were patients who did not receive curative-intent treatments and those with endoscopic or local tumor destruction only, with unknown or no surgery, or without information regarding the nature or timing of systemic chemotherapy. To further minimize bias, the study excluded patients younger than the Medicare-eligible age of 65 years, patients older than 75 years, patients who received postoperative systemic chemotherapy more than 6 months following surgery, and patients who received chemotherapy before surgery (**Figure 1**).

The study cohort with young-onset colon cancer included 13 102 patients diagnosed between ages 18 and 49 years, reflecting the population diagnosed before the screening age of 50 years (Figure 1). The comparative cohort included 37 007 patients diagnosed as having later-onset colon cancer aged 65 to 75 years, reflecting the age segment around 71 years, the median age at colon cancer diagnosis in the United States.[21] Patient factors included sex, race/ethnicity, median household income, insurance status, and year of diagnosis. Comorbid conditions as described by Deyo et al[22] were mapped from reported *International Classification of Diseases, Ninth Revision, Clinical Modification* secondary diagnosis codes in the NCDB as previously described.[23]

Tumor factors included histologic grade, location, and pathological stage.[22,24] Disease stage was determined according to the American Joint Committee on Cancer's sixth edition of the *Cancer Staging Manual*,[25] reflective of the study period. Stage II disease was further categorized as low risk vs high risk, with the latter defined by the National Comprehensive Cancer Network[26] as T4, poorly differentiated histology (G3), perforation, positive margin status, and fewer than 12 nodes retrieved during surgical lymphadenectomy.

Treatment modalities were examined, including surgical resection and postoperative systemic chemotherapy. Surgical procedures were coded as segmental colectomy, total colectomy or proctocolectomy, and other or multivisceral resection. All patients in this study underwent surgical treatment. Chemotherapy regimens were categorized as single agent (typically 5-fluorouracil based) vs multiagent (typically oxaliplatin or irinotecan hydrochloride based).[26] Treatment facility was categorized as a community cancer program, comprehensive community cancer program, or academic or research program (eg, National Cancer Institute–designated comprehensive cancer centers).[27] Unclassified facilities or other facilities were excluded (Figure 1).

Outcome Measures

The primary end point was relative survival, an established method of survival analysis in large patient registries. *Relative survival* is defined as the ratio of observed survival (all causes of death) for a cohort of patients with cancer to the expected survival of a comparable cohort of the general population without cancer. It provides an objective measure of survival among patients with cancer, adjusting for baseline mortality rates and independent of the data on cause of death.[28-30] A secondary end point was the likelihood of receiving postoperative systemic chemotherapy.

Statistical Analysis

Descriptive statistics included the median and interquartile range for continuous variables and the number and frequency for discrete variables. χ^2 Test was used to compare categorical variables by age group (18-49 years and 65-75 years). Multivariable logistic regression models assessed the association between age groups and receipt of systemic chemotherapy, adjusting for all other patient and tumor factors. Odds ratios (ORs) with 95% CIs were generated.

Relative survival was determined from the year of diagnosis by calculating the ratio of observed survival to expected survival rates of the similar sex- and age-matched US population.[28] Population survival data were obtained from the Human Mortality Database.[31] Five-year relative survival rates and 95% CIs were calculated and stratified by age group and by disease stage. The effect of young age on relative survival was analyzed by multivariable relative survival analysis for each disease stage using generalized linear models and assuming a Poisson distribution for the observed number of deaths.[32] Multivariable relative survival models were further stratified by receipt of chemotherapy. Adjusted relative risk of death was expressed as relative risk with a 95% CI. All reported *P* values were 2-sided, and $P < .05$ was considered statistically significant. Bonferroni adjustment for multiple comparisons of patient characteristics did not alter statistical significance. All statistical analyses were performed with a software program (STATA 11 MP; StataCorp LP).

Results

Patient and Tumor Factors Associated With Young-Onset and Later-Onset Colon Cancer

More patients with young-onset vs later-onset colon cancers were of nonwhite race/ethnicity and had no health insurance. We also observed variations in the median household income and in the region of residence. Most patients were healthy, with a Charlson-Deyo Comorbidity Index of 1 or less (**Table 1**).

More young-onset colon cancers were initially seen with nodal or distant metastases: 36.5% and 25.3% of young-onset tumors were stage III and stage IV, respectively, while 30.3% and 15.7% of later-onset tumors were stage III and stage IV, respectively ($P < .001$) (Table 1). Young-onset colon cancer had a propensity toward the distal colon, while later-onset colon cancer was seen more frequently in the proximal colon. Poor differentiation and signet ring cell and mucinous features were slightly more common among young-onset cases.

Younger patients were more frequently treated at academic or research facilities than at community cancer programs (Table 1). Surgical resection was performed in all patients in this study. However, postoperative systemic chemotherapy was administered in 66.3% of young adults with colon cancer but in only 39.8% of the older patients.

Oncologic Treatments: Stage-Specific Adjusted Multivariable Analysis

After adjusting for patient and tumor factors as well as disease stage, young adults remained much more likely to receive chemotherapy in each stage (**Table 2**). Specifically, adjuvant chemotherapy is not the standard of care in stage II disease, but we observed the highest OR for receipt of chemotherapy among young adults, with ORs of 2.88 for stage I, 4.22 for stage II low risk, and 3.93 for stage II overall. Almost 6% of the patients with young-onset stage I disease received adjuvant chemotherapy. Adjuvant chemotherapy was administered to 50.5% of the young patients vs 19.1% of the older patients with stage II low-risk disease.

Furthermore, among patients who received adjuvant chemotherapy, young adults were more likely to receive multiagent regimens (likely oxaliplatin or irinotecan based) rather than single-agent regimens. For patients with stage II, III, and IV disease, these ORs were 1.71, 1.75, and 1.90, respectively (Table 2).

Relative Survival for Young Adults With Colon Cancer: Stage-Specific Adjusted Multivariable Analysis

The median follow-up was 6.3 years (interquartile range, 5.4-7.2 years). The unadjusted survival analysis showed slightly inferior 5-year relative survival for the young adults (0.66 vs 0.69, $P < .001$) (**Figure 2**). However, this trend no longer held in a comparison of patients receiving the same stage-specific treatments, adjusting for patient and tumor factors (**Table 3**).

Table 1. Patient Characteristics, Tumor Factors, and Overall Treatment Patterns Among Young Adults (Ages 18-49 Years at Diagnosis) vs Older Adults (Ages 65-75 Years at Diagnosis) With Colon Cancers Diagnosed Between January 1, 2003, and December 31, 2005[a]

Characteristic	Colon Cancer, No. (%)		χ^2 Statistic	*P* Value
	Young Adults (n = 13 102)	Older Adults (n = 37 007)		
Patient Characteristics				
Sex			3.7	.05
Female	6639 (50.7)	18 389 (49.7)		
Male	6463 (49.3)	18 618 (50.3)		
Race/ethnicity			435.8	<.001
White	10 078 (76.9)	31 423 (84.9)		
African American	2210 (16.9)	4017 (10.9)		
Other	814 (6.2)	1567 (4.2)		
Insurance status			4119.9	<.001
Insured	10 428 (79.6)	35 540 (96.0)		
Medicaid, Medicare, or government	1196 (9.1)	485 (1.3)		
Uninsured	1007 (7.7)	223 (0.6)		
Unknown	471 (3.6)	759 (2.1)		
Median household income quartile, $			110.9	<.001
<30 000	1837 (14.0)	5212 (14.1)		
30 000 to <35 000	2081 (15.9)	6712 (18.1)		
35 000-45 999	3230 (24.7)	10 106 (27.3)		
≥46 000	5167 (39.4)	12 990 (35.1)		
Unknown	787 (6.0)	1987 (5.4)		
Charles-Deyo Comorbidity Index			2120.6	<.001
0	11 748 (89.7)	25 722 (69.5)		
1	1172 (8.9)	8618 (23.3)		
2	182 (1.4)	2667 (7.2)		
Tumor Characteristics				
Disease stage at diagnosis			1181.0	<.001
I	1926 (14.7)	8991 (24.3)		
II	3083 (23.5)	11 011 (29.8)		
III	4780 (36.5)	11 202 (30.3)		
IV	3313 (25.3)	5803 (15.7)		
Location			705.8	<.001
Proximal to splenic flexure	5234 (39.9)	19 781 (53.5)		
Distal to splenic flexure	7380 (56.3)	16 163 (43.7)		
Other or unspecified	488 (3.7)	1063 (2.9)		
Pathological stage			104.3	<.001
Well differentiated or moderately differentiated	9576 (73.1)	28 616 (77.3)		
Poorly differentiated or undifferentiated	2869 (21.9)	7005 (18.9)		
Unknown	657 (5.0)	1386 (3.7)		
Histologic grade			116.9	<.001
Nonmucinous adenocarcinoma	11 221 (85.6)	32 433 (87.6)		
Signet ring cell	314 (2.4)	415 (1.1)		
Mucinous	1567 (12.0)	4159 (11.2)		
Overall Treatments				
Treatment facility			358.8	<.001
Community cancer program	2090 (16.0)	7479 (20.2)		
Comprehensive community cancer program	6733 (51.4)	20 452 (55.3)		
Academic or research program, such as comprehensive cancer centers	4279 (32.7)	9076 (24.5)		
Use of postoperative systemic chemotherapy			2719.4	<.001
No	4419 (33.7)	22 270 (60.2)		
Yes	8683 (66.3)	14 737 (39.8)		
Single-agent regimen	2047 (15.6)	4959 (13.4)		
Multiagent regimen	5611 (42.8)	7818 (21.1)		
Unknown regimen	1025 (7.8)	1960 (5.3)		

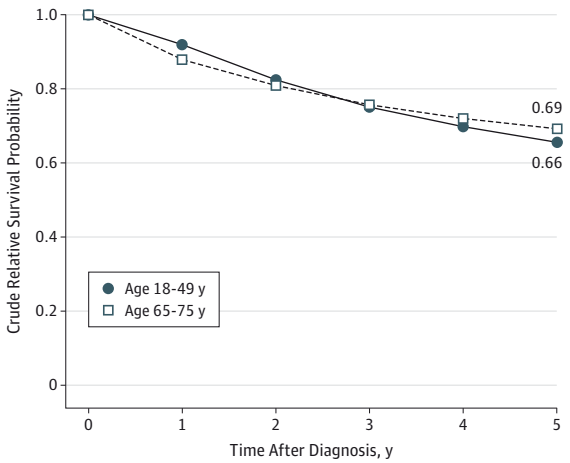
[a] Percentages are column percentages.

Table 2. Likelihood of Receiving Postoperative Systemic Chemotherapy and Multiagent Regimens for Young Adults (Ages 18-49 Years at Diagnosis) vs Older Adults (Ages 65-75 Years at Diagnosis) With Colon Cancers[a]

Patients Who Received Chemotherapy	Any Chemotherapy, No. (%)	Odds Ratio for Receiving Chemotherapy (95% CI)	Multiagent Regimens, No. (%)	Odds Ratio for Receiving Multiagent Regimen (95% CI)
Stage I				
Ages 65-75 y (n = 8991)	162 (1.8)	1 [Reference]	52 (43.0)	1 [Reference]
Ages 18-49 y (n = 1926)	109 (5.7)	2.88 (2.21-3.77)	43 (48.3)	1.38 (0.71-2.68)
Stage II Overall				
Ages 65-75 y (n = 11 011)	2748 (25.0)	1 [Reference]	773 (41.7)	1 [Reference]
Ages 18-49 y (n = 3083)	1732 (56.2)	3.93 (3.58-4.31)	670 (54.9)	1.71 (1.48-1.97)
Stage II Low Risk				
Ages 65-75 y (n = 4822)	923 (19.1)	1 [Reference]	313 (39.6)	1 [Reference]
Ages 18-49 y (n = 1636)	826 (50.5)	4.22 (3.70-4.81)	388 (52.5)	1.67 (1.34-2.09)
Stage II High Risk				
Ages 65-75 y (n = 6189)	1825 (29.5)	1 [Reference]	677 (42.7)	1 [Reference]
Ages 18-49 y (n = 1447)	906 (62.6)	3.69 (3.23-4.20)	454 (57.0)	1.77 (1.46-2.14)
Stage III				
Ages 65-75 y (n = 11 202)	8175 (73.0)	1 [Reference]	4209 (59.4)	1 [Reference]
Ages 18-49 y (n = 4780)	4132 (86.4)	2.42 (2.18-2.68)	2590 (71.5)	1.75 (1.58-1.93)
Stage IV				
Ages 65-75 y (n = 5803)	3652 (62.9)	1 [Reference]	2567 (80.4)	1 [Reference]
Ages 18-49 y (n = 3313)	2710 (81.8)	2.74 (2.44-3.07)	2136 (88.6)	1.90 (1.60-2.26)

[a] Shown are the results of stage-specific multivariable linear regression. Odds ratios refer to the likelihood for a patient with young-onset colon cancer to receive chemotherapy relative to a patient with later-onset disease. Adjusted for year of diagnosis, sex, race/ethnicity, median household income quartile, insurance status, location, comorbidities, tumor stage, tumor location, tumor histology, tumor pathology, and treatment facility. Percentages are row percentages.

Figure 2. Crude Relative Survival of Young Adults (Ages 18-49 Years at Diagnosis) vs Older Adults (Ages 65-75 Years at Diagnosis) With Colon Cancers



The unadjusted survival analysis showed slightly inferior 5-year relative survival for the young adults (0.66 vs 0.69, $P < .001$).

Young vs older patients with stage I colon cancer treated with surgery alone were also compared. The adjusted 5-year relative survival was more favorable for younger patients.

For young vs older patients with stage II disease treated with surgery alone, young adults again showed more favorable survival (86.9% vs 82.3%) (Table 3), particularly for those with low-risk disease. On the other hand, the survival of young adults treated with surgery plus adjuvant chemotherapy did not significantly differ from that of their older counterparts. The 5-year relative survival of young adults vs older adults was 91.1% vs 90.2% for stage II overall, 95.2% vs 95.4% for stage II low risk, and 87.7% vs 85.8% for stage II high risk (**Figure 3**).

In stage III and IV disease, young patients who received postoperative systemic chemotherapy demonstrated only marginally more favorable survival outcomes than older patients who received the same treatments. These ORs were 0.89 for stage III and 0.84 for stage IV (Figure 3).

Discussion

Colon cancer is increasing among adults younger than 50 years.[3,4,6] The objective of this study was to define the prognosis of young adults with colon cancer outside of the clinical trials setting, adjusting for significant age-related variations in disease stage and in treatment administration using real-life data across the United States. In this largest such comparative cohort study to date, we demonstrated that young adults are 2 to 4 times more likely to receive systemic chemotherapy after surgical resection than older patients in each disease stage, including stage I and stage II low risk, for which adjuvant therapy is not the standard of care. In particular, young adults were more likely to receive multiagent oxaliplatin-based or irinotecan-based regimens. Moreover, these more intense treatments did not result in significant survival gains relative to those of their older counterparts. This mismatch in oncologic treatment administration vs relative survival highlights overtreatment of young adults with colon cancer and the potential for increased risks of treatment-associated toxicities for young cancer survivors.

To our knowledge, this is the largest study to date examining the relative survival of young adults with colon cancer in a large nationwide cohort that reflects real-life practices out-

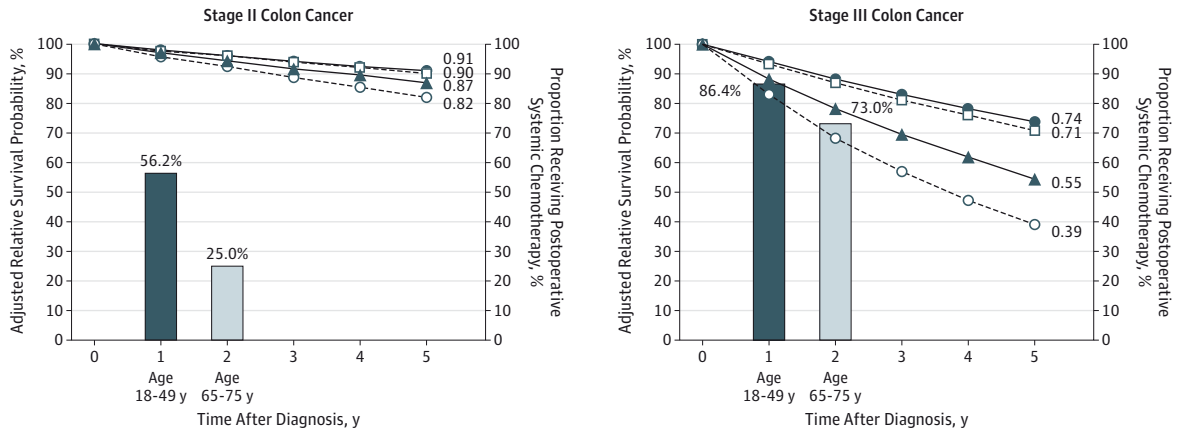
Table 3. Relative Survival of Young Adults (Ages 18-49 Years at Diagnosis) vs Older Adults (Ages 65-75 Years at Diagnosis) With Colon Cancers[a]

	Surgery			Surgery Plus Postoperative Systemic Chemotherapy		
Patients	No. (%)	Adjusted Relative Risk (95% CI)	Adjusted 5-Year Relative Survival, %	No. (%)	Adjusted Relative Risk (95% CI)	Adjusted 5-Year Relative Survival, %
Stage I						
Ages 65-75 y (n = 8991)	8829 (98.2)	1 [Reference]	96.8	NA	NA	NA
Ages 18-49 y (n = 1926)	1817 (94.3)	0.49 (0.29-0.85)	98.4	NA	NA	NA
Stage II Overall						
Ages 65-75 y (n = 11 011)	8263 (75.0)	1 [Reference]	82.3	2748 (25.0)	1 [Reference]	90.2
Ages 18-49 y (n = 3083)	1351 (43.8)	0.72 (0.58-0.88)	86.9	1732 (56.2)	0.90 (0.69-1.17)	91.1
Stage II Low Risk						
Ages 65-75 y (n = 4822)	3899 (80.9)	1 [Reference]	89.2	923 (19.1)	1 [Reference]	95.4
Ages 18-49 y (n = 1636)	810 (49.5)	0.60 (0.41-0.87)	93.3	826 (50.5)	1.03 (0.53-2.00)	95.2
Stage II High Risk						
Ages 65-75 y (n = 6189)	4364 (70.5)	1 [Reference]	74.6	1825 (29.5)	1 [Reference]	85.8
Ages 18-49 y (n = 1447)	541 (37.4)	0.80 (0.63-1.02)	78.9	906 (62.6)	0.85 (0.64-1.13)	87.7
Stage III						
Ages 65-75 y (n = 11 202)	3027 (27.0)	1 [Reference]	39.1	8175 (73.0)	1 [Reference]	71
Ages 18-49 y (n = 4780)	648 (13.6)	0.64 (0.55-0.74)	54.7	4132 (86.4)	0.89 (0.81-0.97)	73.7
Stage IV						
Ages 65-75 y (n = 5803)	2151 (37.1)	1 [Reference]	1.6	3652 (62.9)	1 [Reference]	16
Ages 18-49 y (n = 3313)	603 (18.2)	0.64 (0.57-0.71)	6.9	2710 (81.8)	0.84 (0.79-0.90)	21.1

Abbreviation: NA, not applicable.

[a] Shown are the results of stage-specific multivariable regression. Values are adjusted for year of diagnosis, sex, race/ethnicity, median household income quartile, insurance status, location, comorbidities, tumor stage (overall and low-risk and high-risk features for stage II), tumor location, tumor histology, tumor pathology, and treatment facility. Percentages are row percentages. Patients with stage I disease who received postoperative systemic chemotherapy were too few for meaningful analysis (162 patients aged 65-75 years at diagnosis and 109 patients aged 18-49 years at diagnosis).

Figure 3. Adjusted Relative Survival of Young Adults (Ages 18-49 Years at Diagnosis) vs Older Adults (Ages 65-75 Years at Diagnosis) With Colon Cancers Who Both Received Systemic Chemotherapy (Top 2 Curves) or Both Did Not Receive Systemic Chemotherapy (Bottom 2 Curves)



Solid curves indicate young adults, and dotted curves indicate older adults. Interposed vertical bars indicate the overall proportions of young adults (solid bar) vs older adults (dotted bar) who received systemic chemotherapy.

side of the clinical trials setting, allowing for multivariable adjustments. We corroborate previous findings of unique phenotypic features in young-onset colon cancer, including a higher incidence of left-sided cancers, more frequent poor-risk histologic features, and more nodal or distant metastases at presentation.[4,6,9-11] At first glance, our crude unadjusted survival analysis showed poorer prognosis for young patients. However, the significantly more advanced stages at diagnosis among young adults (an unscreened population) cannot be overemphasized. Indeed, after adjusting for disease stage, their prognosis was equivalent or slightly better compared with older adults, consistent with other studies.[8,9,16] Another population-based study[9] compared 1334 young patients (ages 20-40 years) and 46 457 older patients (ages 60-80 years) with colon can-

cer. That study found similar survival for stage I and stage III disease but better survival for stage II and stage IV disease among the young, although the findings were not adjusted for differences in comorbidities, treatments, or baseline mortality rates. Our results suggest that the prognostic effect of young age must be interpreted after adjusting for age-related disparities in patient, tumor, and treatment factors.

Prior disparities investigations have mostly focused on the elderly, suggesting possible undertreatment, and did not examine young adults with cancer.[33] We found that almost 6% of the young adults with stage I disease and more than half of those with stage II disease (regardless of low or high risk) received postoperative systemic chemotherapy. These practices represent overtreatment because current evidence does not support chemotherapy in stage I disease and indicates a controversial role of chemotherapy in stage II disease.[26] Indeed, these observations corroborate prior single-institution studies[10,13] showing that young adults with rectal cancer receive more chemotherapy and pelvic irradiation and that young patients with colon cancer receive more adjuvant therapy, even for node-negative disease.

Thus far, data regarding chemotherapy in young adults with colon cancer have been limited to those from clinical trials.[15,16] We found that young adults were more likely to receive multiagent regimens at all stages of disease (Table 2). Indeed, patient demands, physician attitudes, or the perceived ability for young adults to tolerate more treatment may have driven these practices. However, although more young patients were subjected to the intense regimens, their relative survival was equivalent or only marginally more favorable than that of the older patients. The potential for treatment-related toxicities cannot be overlooked. Long-term data from the National Surgical Adjuvant Breast and Bowel Project C-07 trial and the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer have shown a 10% to 15% rate of persistent peripheral sensory neuropathy and a 3% rate of persistent toxicities that interfere with activities of daily living after multiagent chemotherapy.[34-37] In summary, in the absence of clear superiority in treatment efficacy, a large proportion of young patients are being subjected to treatments with potential long-term toxicity. The long-term effect of this practice pattern on the experience of cancer survival among young adults with colon cancer warrants investigation.

Our study has some limitations. First, tumor molecular characteristics and long-term toxicity data were not available in the nationwide cancer registry. One may postulate that young patients disproportionately received multiagent (rather than 5-fluorouracil only) chemotherapy because their tumors were mostly mismatch repair deficient.[38,39] However, mismatch repair deficiency and Lynch syndrome account at most for only 20% of all colon cancers before age 50 years.[40-42] Therefore, mismatch repair status (although not available herein) cannot account for the observed age-related treatment disparity. Second, the survival analysis could not be adjusted for by molecular prognostic biomarkers. *KRAS* and *BRAF* mutations may be prognostically important, but whether their prevalence differs by age has not been definitively established.[43] Third, our data among patients with stage IV disease must be interpreted with significant caution because we included only those who underwent surgical resection of the primary colon cancer. Therefore, they represent a highly select subgroup of patients with stage IV colon cancer.

Conclusions

In conclusion, adults younger than 50 years represent the only population segment in which the CRC incidence is rising. We identified evidence for overtreatment of young adults with colon cancer, particularly those with stage I disease and stage II low-risk disease. On the other hand, the adjusted stage-specific prognosis did not differ (for stage II disease) or was only minimally superior (for stage III and stage IV disease) for young-onset vs later-onset colon cancers. The minimal survival differences were unmatched by the significantly greater patterns of overtreatment in the young. We highlight the potential for lingering treatment-associated toxicities in young cancer survivors and suggest that their potentially unique survivorship warrants specific investigation.

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