RESEARCH ARTICLE

Effect of Age on Survival Outcome in Operated and Non-Operated Patients with Colon Cancer: A Population-Based Study

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Abstract

Objective

To know the effect of age on survival outcome in operated and non-operated patients with colon cancer.

Methods

From the Surveillance, Epidemiology, and End Results database, we identified 123,356 patients with colon cancer who were diagnosed between 1996 and 2005, grouped them as older or younger than 40 years and analyzed their 5-year cancer-specific survival (CSS) data, along with some risk factors, using Kaplan–Meier methods and multivariable Cox regression models.

Results

The younger group had significantly higher pathological grades (*P*<0.001), more mucinous and signet-ring histology (*P*<0.001), advanced AJCC stage (*P*<0.001), and were more likely to undergo surgery (*P*<0.001). For surgically treated patients, age did not significantly affect 5-year CSS (younger: 66.7%; older: 67.3%; *P* = 0.86). Further analysis showed that age was an independent prognostic factor in stage I–IV disease (stage I: *P* = 0.001; *P*<0.001 for stages II–IV, in both uni- and multivariate analyses), but not for patients with unknown disease stage (*P* = 0.52). For non-surgically treated patients, age significantly affected 5-year CSS (younger: 16.2%; older: 12.9%; *P*<0.001) in univariate analysis; and was an independent prognostic factor (*P*<0.001) in multivariate analysis.

Conclusion

The CSS rate for younger CC patients was at least as high as for older patients, although they presented with higher proportions of unfavorable factors and more advanced disease.

Introduction

Colon cancer (CC) is one of the most common malignancies; combined with rectal cancer, it is the second leading cause of cancer-associated mortality in the United States [1, 2]. Generally, CC is thought to be a malignancy that mainly occurs in patients older than 50 years of age [3]. Despite the 2012 Annual Report to the Nation on Cancer report of a steady decline in the incidence of colorectal cancer (CRC) in the United States [4], its incidence among younger patients is disproportionately increasing, with an annual incidence increase of 2.6% in rectal cancer vs 0.2% in colon cancer [5–7]. In younger patients, CC is more likely to be diagnosed in later stages, and to be mucinous or poorly differentiated tumors, including signet ring carcinoma [8–11]. However, mixed results have been reported with regard to prognoses, with some studies indicating poorer outcomes for younger patients [12–15], and others showing their survival rates to be at least as favorable as their older counterparts [16–19]. A complication in our understanding of young-onset CC is the fact that most published studies on young-onset colorectal cancer (CRC) analyzed both colon and rectal cancer together, were limited by relatively small sample sizes or single referral centers, and/or did not adjust for potential confounding factors. Moreover, most previous studies' inclusion criteria were limited by surgical resection, but did not consider the prognostic significance of age on non-operated patients. To further refine a comprehensive analysis of colon cancer in younger patients at a national, population-based level, we used data from the Surveillance, Epidemiology and End Results (SEER) registries to (a) focus on the clinicopathological features in younger patients, and (b) analyze the role of age in colon cancer-specific survival (CCSS) while controlling for disease factors and treatment factors.

Materials and Methods

Patients

The SEER program collects data on the most recent cancer incidence, prevalence, mortality, and survival data from 17 population-based cancer registries that represent approximately 28% of the US population [20]. SEER data contain no identifiers and are publicly available for studies of cancer-based epidemiology, health policy, and survival analysis. The National Cancer Institute's SEER*Stat software (Surveillance Research Program, National Cancer Institute SEER*Stat software, www.seer.cancer.gov/seerstat Version 8.1.2) was used to identify patients who were diagnosed with invasive CC (C18.0–19.9) between 1996 and 2005. Only patients aged between 15 and 80 years were included. Patients were excluded if they had in situ TMN staging, or had another primary tumor besides colon cancer. Histology types were limited to adenocarcinoma (8150/3, 8210/3, 8261/3, 8263/3), mucinous adenocarcinoma (8480/3), and signet-ring cell carcinoma (8490/3). Tumor-node-metastasis classifications were based on the criteria of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (7th edition, 2010), by which criteria patients were restaged. Age, sex, race, histological type, AJCC stage, and CCSS were analyzed. Because the SEER data contain no adjuvant chemotherapy information, adjuvant chemotherapy was not assessed. The primary endpoint of the study was CCSS, which was calculated as the time between diagnosis and CC-specific death. Deaths caused by CC were treated as events; living patients or deaths from other causes were censored data.

Ethics Statement

This study was based on the free public SEER database, which is an authoritative source of information on cancer incidence and survival in the United States. All relevant data were

obtained from SEER*Stat (http://seer.cancer.gov/data/options.html). Requests for data access can be sent by following the instructions on that website. Permission to access the research data files was obtained with the reference number 11375-Nov2014. The study contained no personal identifying information and required no informed consent. Anonymous patient's data were extracted from online SEER registries, which require no further institutional review approval prior to use. The study was approved by the Review Board of Nanjing Medical University, Nanjing, China.

Statistical Analysis

The relation of age (younger vs older) with clinicopathological features was analyzed by chi-square ($\chi 2$) test. Comparisons of continuous variables between two groups were completed using Student's t-test. Survival was analyzed based on age (younger vs older) and was stratified by AJCC stages I–IV, or unknown stage. Survival curves were provided by Kaplan–Meier estimates; differences between two groups were analyzed by log-rank test. Multivariate Cox regression models were performed to evaluate risk factors for survival outcomes. All statistical analyses were completed using the statistical software Statistical Package for Social Sciences (SPSS) for Windows, version 17 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered significant.

Results

Clinicopathological differences between younger and older groups

We identified 123,356 eligible patients with CC in the SEER database during the 10-year study period (1996–2005), of whom 63,436 (51.4%) were males and 59,920 (48.6%) were females; and 4,504 (3.6%) were no older than 40 years (younger patients), and 118,852 (96.4%) were older than 40 years (older patients). The median follow up time was 69 months (interquartile range [IQR]: 22–106 months) in the younger group and 65 months (IQR: 18–100 months) in the older group.

Among younger patients, CC was more frequent during 2003–2005 ($P<0.05$) and less frequent among Caucasians ($P<0.001$) than for older patients. Younger patients also had significantly more poorly or undifferentiated tumors ($P<0.001$), more mucinous or signet-ring histologies ($P<0.001$), presented with more advanced AJCC stages (III/IV, $P<0.001$), and underwent more surgery ($P<0.001$). The younger and older groups did not significantly differ by sex ($P = 0.14$; Table 1).

Impact of age on survival outcomes in patients with CC treated with surgery

Overall 5-year CCSS did not significantly differ for the two age groups (younger: 63.4%; older: 63.2%; $\chi^2 = 2.089$, $P = 0.15$, univariate log-rank test), nor did it significantly differ among all patients treated with surgery (younger: 66.7%; older: 67.3%; $\chi^2 = 0.03$; $P = 0.86$; Table 2, Fig 1A). However, when 5-year CCSS was further stratified by disease stage, younger patients who had undergone surgery had significantly better survival than older, surgically treated patients at the same disease stage for stages I–IV (Table 2; Fig 1B–1E). Counterintuitively, among surgically treated patients with unknown disease stages, older patients had a higher 5-year CCSS rate (84.5%) than did younger patients (82.4%) but not significantly so ($P = 0.52$; Table 2, Fig 1F). In multivariate analysis (Cox regression) age was an independent survival factor in stages I–IV (Table 3).

Table 1. Characteristics of patients from the SEER database by age.

Characteristic	Total (n = 123,356)	Younger Group (n = 4504)	Older Group (n = 118,852)	P value
Median follow up (months)	65	69	65	P<0.001
(IQR)	18–100	22–106	18–100	
Years of diagnosis				0.027
1996–2002	76270	2714	73556	
2003–2005	47086	1790	45296	
Sex				0.138
male	63436	2365	61071	
female	59920	2139	57781	
Race				P<0.001
Caucasian	97758	3292	94466	
African-American	14943	674	14269	
Others*	10655	538	10117	
Pathological grading				P<0.001
High/ Moderate	88209	2940	85269	
Poor/ undifferentiated	23607	1136	22471	
Unknown	11540	428	11112	
Histological Type				P<0.001
Adenocarcinoma	107438	3573	103865	
Mucinous/Signet-ring cancer	15918	931	14987	
AJCC stage				P<0.001
I	19996	429	19567	
II	31946	1072	30874	
III	32064	1433	30631	
IV	26512	1199	25313	
Unknown	12838	371	12467	
Surgery performed				P<0.001
Yes	113303	4188	109115	
No	9578	290	9288	
Unknown	475	26	449	

*Including American Indian/AK Native, Asian/Pacific Islander, and unknowns.

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Impact of age on survival outcomes in non-surgically treated patients

In patients not treated with surgery, 5-year CCSS significantly differed by age group (younger: 16.2%; older: 12.9%; χ^2 = 12.760, $P<0.001$; Table 2; Fig 1G). In multivariable analysis, older patients were 1.281 times more likely to die of colon cancer than were younger patients (Table 3).

Discussion

A sharp increase over recent decades in the number of younger patients diagnosed with CC has been reported in several countries [5–7]. Its reported incidence among patients of 20–40 years of age increased by 17% during 1973–1999 [21]. We found that incidence of CC increased more quickly during 2003–2005 than during 1996–2003 (P = 0.03), which indicated a need for the increased incidence in this population to be further investigated with an eye to prevention

Table 2. Univariate analysis of age on colon cancer-specific survival by disease stage.

Variable	n	5-year survival (%)	Log rank χ^2 test	P
Surgery performed				
Age			0.033	0.855
≤40	4188	66.7%		
41–80	109115	67.3%		
Stage I				
Age			10.368	P = 0.001
≤40	427	98.1%		
41–80	19523	94.7%		
Stage II				
Age			56.935	P<0.001
≤40	1068	91.1%		
41–80	30788	83.5%		
Stage III				
Age			27.752	P<0.001
≤40	1427	68.8%		
41–80	30550	62.3%		
Stage IV				
Age			45.775	P<0.001
≤40	972	17.4%		
41–80	18802	11.4%		
Unknown				
Age			0.410	P = 0.522
≤40	294	82.4%		
41–80	9452	84.5%		
No Surgery performed				
Age			12.760	P<0.001
≤40	290	16.2%		
41–80	9288	12.9%		

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and early detection. Previous studies are somewhat complicated by the lack of a standard definition of young CC patients [2, 13, 18, 22–25]. We used the cutoff age of 40 years, in line with most denoted studies, though upper limits have ranged from 30 to 50 years [26–28].

The prognosis of CC in younger patients is controversial. Various studies have reported poorer prognosis among young patients with CC than in older patients. This has been attributed to more advanced disease at diagnosis, tumor stage [13, 14, 29], more mucinous or signet-ring histopathology and poorly differentiated tumors [12, 15]. These patterns were also seen in our study. Although the younger patient group had a significantly higher incidence of inferior prognostic factors, they had better stage-specific 5-year CCSS the older-onset cohort, as shown in both univariate and multivariate analysis. Our results were similar to those of other studies [16–19]. In this study, we analyzed 4,504 younger CC patients over a 10-year time period, using a much larger cohort than any other comparable study. We also excluded patients over age of 80 years for their short life expectation.

In general, surgeons are more inclined to use all therapeutic options in young patients as they are in better health and are more able to tolerate toxicities associated with chemotherapy and suffer from fewer postoperative complications [9, 30–34]. Although studies of equal-access cohorts have shown younger patients with CC present with more advanced disease and higher
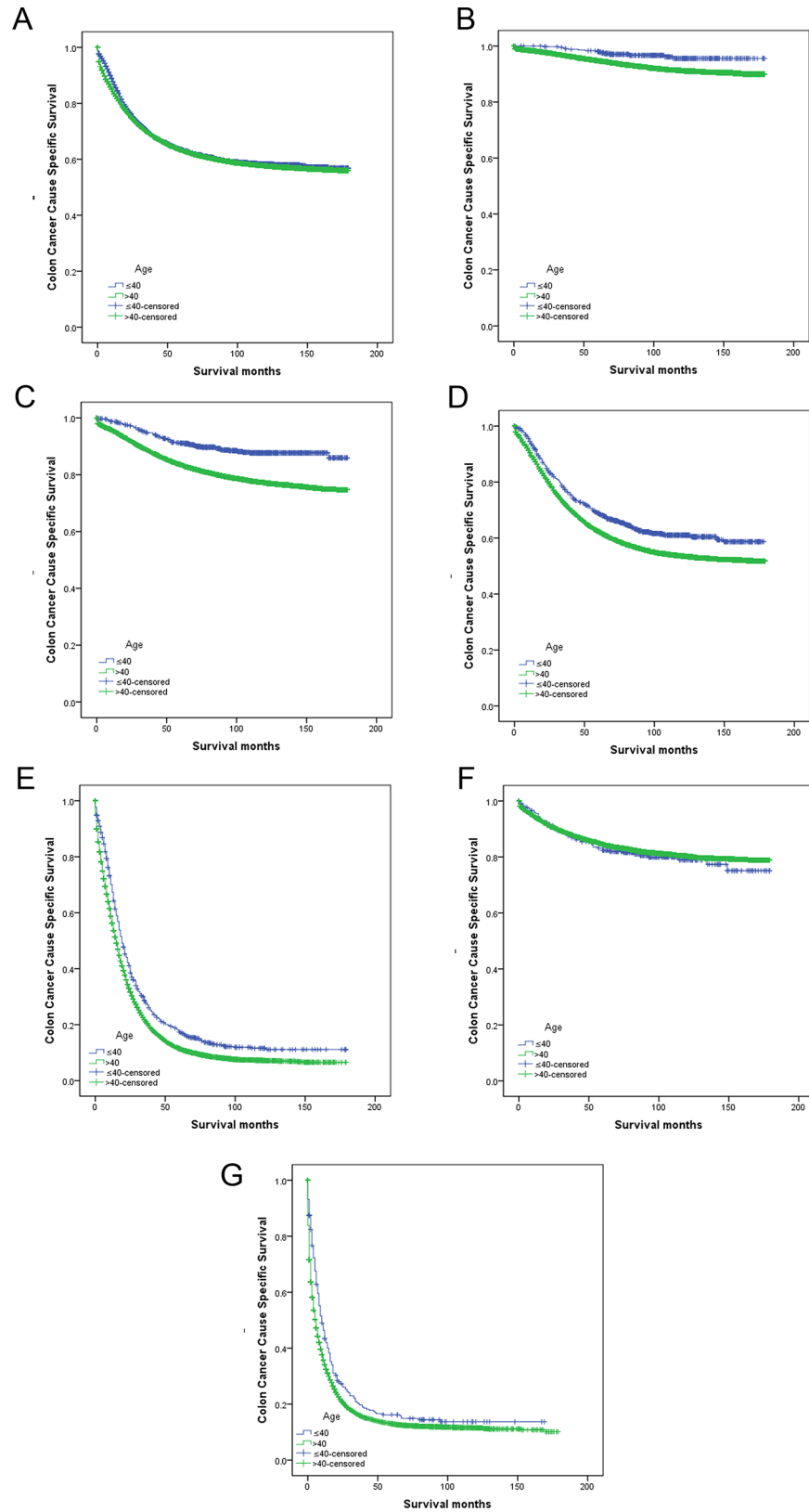
Fig 1. Survival curves for colon cancer patients at younger ($\leq$ 40 years) and older (> 40 years) group.
(A) All patients treated with surgery, $\chi^2 = 0.033$, $P = 0.86$. (B) Stage I colon cancer treated with surgery, $\chi^2 =$

10.368, *P*<0.001. (C) Stage II colon cancer treated with surgery, χ^2 = 56.935, *P*<0.001; (D) Stage III colon cancer treated with surgery, χ2 = 27.752, *P*<0.001. (E) Stage IV colon cancer treated with surgery, χ^2 = 45.775, *P*<0.001. (F) Unknown stage patients treated with surgery, χ2 = 0.410, *P* = 0.52. (G) Patients with colon cancer treated without surgery, χ^2 = 12.760, *P*<0.001.

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rates of disease recurrence, their overall survival exceeds that of older cohorts, which may be partly due to their greater use of adjuvant therapy and more palliative multidisciplinary post-operative treatment [9, 17]. Poor tolerance to treatment because of poor performance status or the presence of other comorbidities may contribute to inferior survival of older patients. Our data also showed that older patients undergo a lower rate of surgery than younger patients, even if their clinicopathological characteristics are relatively good. Patients with stage IV CRC managed with primary tumor resection were shown to have significantly better survival than to those managed with chemotherapy alone [35, 36]. Less aggressive treatments offered to patients with limited comorbidities are likely to affect their outcomes [37]. Younger patients also have a higher proportion of tumors that show microsatellite instability, which may contribute to their better survival. Studies found that patients with MSI tumors are apparently less likely to metastasize lymph nodes and distal organs, regardless of depth of tumor invasion, compared with microsatellite-stable tumors [38–40].

Younger patients who did not undergo surgery still had better 5-year CCSS than older ones. Our analysis of the SEER data, which are nationally representative and use a large, unselected

Table 3. Multivariate Cox model analyses of prognostic factors for colon cancer at different stages.

Variable	Hazard Ratio	95%CI	*P*
Surgery performed			
Stage I			
Age			0.001*
≤40	1.000	Reference	
41–80	2.319	1.394–3.858	
Stage II			
Age			*P*<0.001*
≤40	1.000	Reference	
41–80	1.856	1.544–2.232	
Stage III			
Age			*P*<0.001*
≤40	1.000	Reference	
41–80	1.309	1.198–1.430	
Stage IV			
Age			*P*<0.001*
≤40	1.000	Reference	
41–80	1.288	1.200–1.382	
No Surgery performed			
Age			*P*<0.001**
≤40	1.000	Reference	
41–80	1.281	1.124–1.459	

P values refer to comparison between two groups.

*Adjusted for years of diagnosis, sex, age, race, pathological grading, tumor histology and number of dissected lymph nodes, as covariates

** Adjusted for years of diagnosis, sex, age, race, pathological grading, tumor histology and AJCC stage as covariates.

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group of patients with no surgical therapy, showed that younger patients had better 5-year CCSS than older ones. Although a clinical trial showed that survival of patients with advanced CRC was significantly increased when incorporating new therapeutic agents [41], a meta-analysis of randomized clinical trials of newer chemotherapy agents between 1995 and 2004, which compared younger and older patients with advanced CRC, showed similar survival in both groups[42]. Patients enrolled in clinical trials are always strictly selected and under intense supervision, which may explain their inconsistent results from ours. This study adds to current knowledge by answering more in-depth research questions about age and prognosis through analysis of population-based data from the large SEER database. However, it has several potential limitations. First, the SEER database lacks important information on tumor characteristics and specific cancer therapies, such as perineural invasion, lymphovascular invasion, neoadjuvant or adjuvant therapy, quality of surgery, etc. Thus, our study could not adjust for these potential confounding factors. Second, SEER data do not separate surgeries with palliative intent from those with curative intent. Thus, the beneficial effect of surgery on survival may be underestimated, specifically those received radical resection. Finally, the SEER database does not include information on comorbidities, which limits our ability to calculate their effect on CCSS. Despite these potential limitations, there are many merits to this population-based study. First, we can analyze 123,356 patients with colon cancer during a 10-year time period, much larger than any other homologous study. Second, the SEER database is nationally representative, because its registries cover 28% of the United States population, which is ethnically and socioeconomically diverse. Consequently, these finding may be generalizable to the entire United States.

In summary, patients with CC who are aged 40 and younger have higher CCSS rates than their older counterparts, both after surgery by stage, and among those who are not treated with surgery. Clinicians should consider age in their assessments and treatment decisions for patients with CC.

Acknowledgments

Author Contributions

Conceived and designed the experiments: ZHJ ZNF. Analyzed the data: ZHJ XHW XMT. Contributed reagents/materials/analysis tools: XHW ZNF. Wrote the paper: ZHJ XHW XMT ZNF.

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