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Original Article

Age-related disparity in patients with colorectal cancer: a population-based study from SEER program

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Abstract: Background & Aims: To analyze the age-related disparity in patients with colorectal cancer (CRC). Methods: Using data obtained by the Surveillance, Epidemiology, and End Results (SEER) program from 2000-2013, a retrospective, population-based cohort study was conducted to investigate age-specific differences in various characteristics, overall survival (OS) and disease-specific mortality (DSM). Results: A total of 262372 CRC patients (2739 patients with age < 35 years, 23094 in 35-49 group, 74605 in 50-64 group and 161934 in ≥ 65 group) were eligible for this study. Patients with age ≥ 65 were more likely to be female and white (each P < 0.01). And the older patients were more likely to be lower in grade, earlier in stage, smaller in size, have less lymph node and distant metastases (each P < 0.05). Further, the older patients were more likely to primary derive from Cecum, Ascending, Hepatic Flexure and Transverse patterns (P < 0.05). The younger patients were more likely to diagnose liver metastasis than the older, whereas the older cases were less likely to appeared lung metastases compared to the younger (P < 0.05). At the follow-up period, patients with age ≥ 65 had an OS of 44.3%, while patients in the < 35 group had an OS of 66.2% (P < 0.05). Further, the DSM rate was 31.4% within the ≥ 65 group compared with 29.6% within the < 35 group (P < 0.05). In the multivariate analysis, age, sex, race, grade, stage, location, T, N and M were significantly associated with OS and DSM. Conclusions: The older patients diagnosed with CRC were at significantly greater risk of OS and DSM. In addition, the younger patients were more likely to diagnose liver metastasis than the older, whereas the older cases were less likely to appeared lung metastases compared to the younger.

Keywords: Colorectal cancer, age-related disparity, SEER program

Introduction

Colorectal cancer (CRC) is the fifth most commonly diagnosed cancer in the China, constituting up to 37.63% of all cancers [1, 2]. Owing to its typically slow development, there is a large potential for reducing the burden of the disease by early detection and removal of precancerous lesions or early cancer stages. It has been well established that CRC carries high risk typically ranging from 50 to 60 years for the population and older CRC patients have a compromised survival rate compared to younger cases [3, 4]. Further, the inherent prognosis, potential for treatment response and metastatic patterns may differ within different age groups. But whether or not there exists any age-related variation in CRC outcomes has yet to be elucidated. Few studies are available exploring the different prognoses of younger and older CRC patients. Limited evidence has provided controversial data related to the impact of age on metastatic patterns of CRC. In the retrospective studies, it is shown that younger patients present with more advanced disease and higher prevalence of positive family history than do older patients, associated with a different survival rate [5, 6]. However, Quah et al observed younger patients undergoing complete resection of stage I-III colon cancer had disease-specific survival similar to older patients [7].

Given that patient management depend on prognostic variables, we used data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program to analyze the association of age groups with overall survival (OS), disease-specific mortality (DSM) and metastatic patterns diagnosed with CRC.

Table 1. Patient characteristics within subgroups

Variables	< 35 y N = 2739 (1.0%)	35-49 y N = 23094 (8.8%)	50-64 y N = 74605 (28.4%)	≥ 65 y N = 161934 (61.7%)	P
Follow-up (months)	42.74±36.08	45.80±36.36	44.78±36.93	36.51±35.19	
Sex					P < 0.001
Female	1308 (47.8)	10741 (46.5)	31625 (42.4)	82116 (50.7)	
Male	1431 (52.2)	12353 (53.5)	42980 (57.6)	79818 (49.3)	
Race					P < 0.001
White	2059 (75.2)	17021 (73.7)	56317 (75.5)	133752 (82.6)	
Black	351 (12.8)	3388 (14.7)	10970 (14.7)	15515 (9.6)	
Other	304 (11.1)	2545 (11.0)	6886 (9.2)	12125 (7.5)	
Unknown	25 (0.9)	140 (0.6)	432 (0.6)	542 (0.3)	
Grade					P < 0.001
Well	137 (5.0)	1287 (5.6)	4785 (6.4)	10770 (6.7)	
Moderately	1712 (62.5)	15575 (67.4)	50772 (68.1)	106576 (65.8)	
Poorly	593 (21.7)	3937 (17.0)	11270 (15.1)	28020 (17.3)	
Undifferentiated	57 (2.1)	324 (1.4)	1025 (1.4)	2602 (1.6)	
Unknown	240 (8.8)	1971 (8.5)	6753 (9.1)	13966 (8.6)	
Stage					P < 0.001
I	243 (8.9)	2580 (11.2)	11480 (15.4)	28189 (17.4)	
II	541 (19.8)	4860 (21.0)	17017 (22.8)	43820 (27.1)	
III	876 (32.0)	7055 (30.5)	20115 (27.0)	36940 (22.8)	
IV	733 (26.8)	5958 (25.8)	17001 (22.8)	26507 (16.4)	
Unknown	346 (12.6)	2641 (11.4)	8992 (12.1)	26478 (16.4)	
T					P < 0.001
T0	3 (0.1)	27 (0.1)	114 (0.2)	244 (0.2)	
Tis	18 (0.7)	163 (0.7)	745 (1.0)	1633 (1.0)	
T1	195 (7.1)	1710 (7.4)	6808 (9.1)	14507 (9.0)	
T2	212 (7.7)	2304 (10.0)	8452 (11.3)	19602 (12.1)	
T3	1386 (50.6)	11774 (51.0)	35975 (48.2)	74721 (46.1)	
T4	460 (16.8)	3496 (15.1)	10306 (13.8)	19648 (12.1)	
Unknown	465 (17.0)	3620 (15.7)	12205 (16.4)	31579 (19.5)	
N					P < 0.001
N0	958 (35.0)	9026 (39.1)	33825 (45.3)	83157 (51.4)	
N1	744 (27.2)	6407 (27.7)	18782 (25.2)	32781 (20.2)	
N2	626 (22.9)	4517(19.6)	11528 (15.5)	18370 (11.3)	
Unknown	411 (15.0)	3144 (13.6)	10470 (14.0)	27626 (17.1)	
M					P < 0.001
M0	1691 (61.7)	14761 (63.9)	49449 (66.3)	112608 (69.5)	
M1	733 (26.8)	5958 (25.8)	17001 (22.8)	26507 (16.4)	
Bone	18 (0.7)	119 (0.5)	444 (0.6)	515 (0.3)	
Brain	3 (0.1)	25 (0.1)	103 (0.1)	138 (0.1)	
Liver	261 (9.5)	1920 (8.3)	5588 (7.5)	7566 (4.7)	
Lung	72 (2.6)	564 (2.4)	1871 (2.5)	2593 (1.6)	
Unknown	315 (11.5)	2375 (10.3)	8155 (10.9)	22819 (14.1)	
Location					P < 0.001
Appendix	42 (1.5)	178 (0.8)	419 (0.6)	540 (0.3)	
Cecum	213 (7.8)	2083 (9.0)	8889 (11.9)	29556 (18.3)	
Ascending	233 (8.5)	1876 (8.1)	7864 (10.5)	26465 (16.3)	

Hepatic Flexure	91 (3.3)	560 (2.4)	2242 (3.0)	7089 (4.4)	
Transverse	165 (6.0)	1168 (5.1)	4378 (5.9)	12974 (8.0)	
Splenic Flexure	93 (3.4)	603 (2.6)	1997 (2.7)	4387 (2.7)	
Descending	170 (6.2)	1219 (5.3)	3500 (4.7)	7136 (4.4)	
Sigmoid	624 (22.8)	5684 (24.6)	17332 (23.2)	29846 (18.4)	
Rectosigmoid Junction	293 (10.7)	2696 (11.7)	7779 (10.4)	11993 (7.4)	
Rectum	731 (26.7)	6497 (28.1)	18227 (24.4)	26966 (16.7)	
Unknown	84 (3.1)	530 (2.3)	1968 (2.6)	4982 (3.1)	
Status					P < 0.001
Alive	1814 (66.2)	15415 (66.7)	47693 (63.9)	71769 (44.3)	
Dead	925 (33.8)	7679 (33.3)	26912 (36.1)	90165 (55.7)	
Primary cancer	812 (29.6)	6599 (28.6)	20762 (27.8)	50854 (31.4)	
Other	55 (4.2)	16 (4.7)	7 (8.3)	9 (24.3)	

P calculated by Pearson Chi squared testing; Bold if statistically significant, P < 0.05; y: years; T: tumor; Tis: tumor in situ, N: node; M: metastasis.

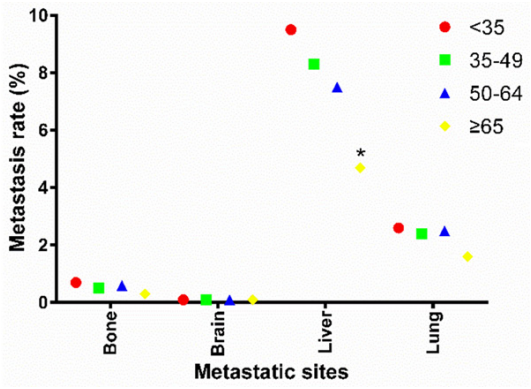

Figure 1. A scatter diagram of metastasis patterns within age groups.

Methods

Data source and study design

We obtained data from the National Cancer Institute's SEER program between 2000 and 2013. We extracted data for all cases of CRC diagnosed between 2000 and 2013. The demographic variables included age at diagnosis (< 35, 35-49, 50-64, > 65 years) and race (white, black, other). The cancer characteristics included stage (I, II, III, IV, unknown), grade (well differentiated, moderately differentiated, poorly differentiated, undifferentiated, unknown), T stage (T0, Tis, T1, T2, T3, T4, unknown), N stage (N0, N1, N2, unknown), distant metastasis (M0, M1, unknown), metastatic sites (bone, brain, liver, lung), location (appendix, cecum, ascending, hepatic flexure, transverse, splenic flexure, descending, sigmoid, rectosigmoid junction, rectum, unknown).

The two main outcomes in our study were OS and DSM. Vitality status was recorded as "alive" or "dead" in the SEER dataset. Survival time (in months) was calculated for each patient using the "Completed Months of Follow-up" option in the SEER database. OS was determined by comparing subgroups who were alive at the end of the study period or who were alive at their last follow-up. DSM was determined by comparing subgroups whose cause of death was due to CRC with cases who were alive at the end of the study period, had died due to other causes, or who were alive at their last follow-up. Cases without survival times were classified as unknown and removed from the study.

Statistical analysis

Patient demographics and cancer-related characteristics were compared within subgroups using Chi square or Fisher's exact tests as appropriate. Within each variable, patients with unknown data were excluded from the comparative analysis. A matched subgroup analysis was performed. OS and DSM were estimated using the weighted Kaplan-Meier method. Multivariate Cox proportional hazard regressions were used to obtain HRs and their respective 95% confidence intervals and show the strength of the estimated relative risk; these approaches were applied to model the relationship between potential covariates and either OS or DSM. All statistical analyses and the charts of OS and DSM were performed using SPSS 19.0 (IBM Corporation, Armonk, NY), and the charts of scattergram were prepared using GraphPad Prism 5.0. Two-sided *p* values less

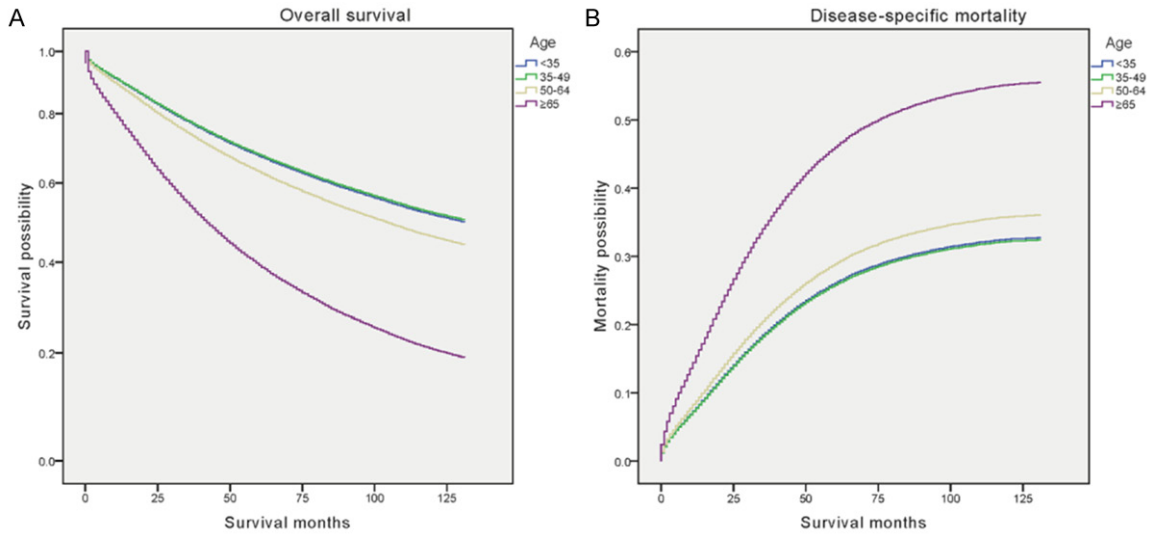

Figure 2. Weighted Kaplan-Meier curves of overall survival (OS) and disease-specific mortality (DSM) in subgroup analyses. OS (A) and DSM (B) are illustrated according to age groups.

than 0.05 were considered statistically significant.

Results

Patient characteristics

A total of 262372 CRC patients were eligible during the 2000-2013 study period. We excluded 3551 patients whose survival times were classified as unknown from the analysis. A total of 2739 patients with age < 35 years, 23094 in 35-49 group, 74605 in 50-64 group and 161934 in ≥ 65 group diagnosed as CRC were available and included in this study.

Differences in patient demographics, cancer characteristics, and outcomes among the subgroups are summarized in **Table 1**. In all, patients with age ≥ 65 were more likely to be female and white (each P < 0.01). Biological tumor characteristics also differed significantly within subgroups. The older patients were more likely to be lower in grade, earlier in stage, smaller in size, have less lymph node and distant metastases (each P < 0.05). Further, the older patients were more likely to primary derive from Cecum, Ascending, Hepatic Flexure and Transverse patterns (P < 0.05). The younger patients were more likely to diagnose liver metastasis than the older, whereas the older cases were less likely to appeared lung metastases compared to the younger (P < 0.05) (**Figure 1**).

Impact of age on OS and DSM

A weighted Kaplan-Meier analysis was used to determine OS and DSM in the groups. Individual survival curves for the four subgroups were generated (**Figure 2**). At the follow-up period, patients with age ≥ 65 had an OS of 44.3%, while patients in the < 35 group had an OS of 66.2% (P < 0.05). Further, the DSM rate was 31.4% within the ≥ 65 group compared with 29.6% within the < 35 group (P < 0.05) (**Table 1**).

We performed multivariate analyses based on the weighted Kaplan-Meier results. All prognostic factors that predicted OS and DSM were included in multivariate analysis (**Table 2**). All the factors predicted DSM were identified as independent prognostic factors (P < 0.05), including sex (male, HR = 1.02 (1.006, 1.035)), race (black, HR = 1.189 (1.164, 1.213)), grade (moderately differentiated, HR = 1.162 (1.122, 1.202); poorly differentiated, HR = 1.592 (1.535, 1.652); undifferentiated, HR = 1.68 (1.579, 1.787)), tumor stage (II, HR = 1.166 (1.108, 1.227); III, HR = 1.683 (1.599, 1.772); IV, HR = 5.273 (5.025, 5.535)), tumor size (T1, HR = 1.190 (1.026, 1.38); T2, HR = 1.228 (1.024, 1.472); T3, HR = 1.258 (1.086, 1.456); T4, HR = 1.965 (1.698, 2.275)), node stage (N1, HR = 1.148 (1.115, 1.181); N2, HR = 1.789 (1.736, 1.844)), distant metastasis (M1, HR = 1.057 (1.004, 1.113)), location (ascend-

Table 2. Cox proportional hazards regression model analysis of overall survival (OS) and disease-specific mortality (DSM)

Variables	OS		DSM	
	aHR (95% CI)	P	aHR (95% CI)	P
Age at diagnosis, y				
< 35	Reference		Reference	
35-49	0.985 (0.92, 1.054)	0.66	0.988 (0.918, 1.063)	0.744
50-64	1.173 (1.098, 1.252)	< 0.001	1.127 (1.051, 1.21)	0.001
≥ 65	2.377 (2.228, 2.537)	< 0.001	2.04 (1.902, 2.187)	< 0.001
Sex				
Female	Reference		Reference	
Male	1.065 (1.053, 1.077)	< 0.001	1.02 (1.006, 1.035)	0.005
Race				
White	Reference		Reference	
Black	1.151 (1.131, 1.17)	< 0.001	1.189 (1.164, 1.213)	< 0.001
Grade				
Well	Reference		Reference	
Moderately	1.103 (1.075, 1.13)	< 0.001	1.162 (1.122, 1.202)	< 0.001
Poorly	1.409 (1.371, 1.448)	< 0.001	1.592 (1.535, 1.652)	< 0.001
Undifferentiated	1.494 (1.421, 1.57)	< 0.001	1.68 (1.579, 1.787)	< 0.001
Stage				
I	Reference		Reference	
II	0.979 (0.945, 1.015)	0.254	1.166 (1.108, 1.227)	< 0.001
III	1.076 (1.036, 1.118)	< 0.001	1.683 (1.599, 1.772)	< 0.001
IV	2.91 (2.809, 3.015)	< 0.001	5.273 (5.025, 5.535)	< 0.001
Location				
Cecum	Reference		Reference	
Ascending	0.973 (0.954, 0.993)	0.009	0.947 (0.922, 0.972)	< 0.001
Hepatic Flexure	0.989 (0.959, 1.02)	0.481	0.986 (0.947, 1.026)	0.493
Transverse	1.04 (1.015, 1.067)	0.002	1.021 (0.988, 11.054)	0.221
Splenic Flexure	1.002 (0.966, 1.039)	0.926	0.995 (0.95, 1.042)	0.824
Descending	0.935 (0.907, 0.963)	< 0.001	0.917 (0.883, 0.953)	< 0.001
Sigmoid	0.908 (0.89, 0.927)	< 0.001	0.897 (0.874, 0.92)	< 0.001
Rectosigmoid Junction	0.93 (0.906, 0.954)	< 0.001	0.925 (0.896, 0.955)	< 0.001
Rectum	0.908 (0.887, 0.954)	< 0.001	0.904 (0.878, 0.93)	< 0.001
Appendix	0.987 (0.905, 1.077)	0.766	1.019 (0.919, 1.131)	0.719
T				
T0	Reference		Reference	
Tis	0.967 (0.846, 1.105)	0.617	0.769 (0.661, 0.896)	0.027
T1	1.019 (0.908, 1.144)	0.746	1.190 (1.026, 1.38)	0.021
T2	1.177 (1.015, 1.267)	0.028	1.228 (1.024, 1.472)	0.001
T3	1.148 (1.024, 1.287)	0.018	1.258 (1.086, 1.456)	0.002
T4	1.667 (1.487, 1.869)	< 0.001	1.965 (1.698, 2.275)	< 0.001
N				
N0	Reference		Reference	
N1	1.157 (1.127, 1.186)	< 0.001	1.148 (1.115, 1.181)	< 0.001
N2	1.656 (1.612, 1.702)	< 0.001	1.789 (1.736, 1.844)	< 0.001
M				
M0	Reference		Reference	
M1	1.087 (1.044, 1.132)	< 0.001	1.057 (1.004, 1.113)	0.035

y: years; T: tumor; Tis: tumor in situ, N: node; M: metastasis. aHR: adjusted hazard ratio (adjusted for age at diagnosis, sex, race, grade, stage, T, N, M, Location).

ing, HR = 0.947 (0.922, 0.972); descending, HR = 0.917 (0.883, 0.953); sigmoid, HR = 0.897 (0.874, 0.92); rectosigmoid junction, HR = 0.925 (0.896, 0.955)). In the multivariate analysis, sex, race, tumor grade, tumor stage, location, tumor size, node stage, distant metastasis were all significantly associated with OS ($P < 0.05$). Among patients, age a 65 was significantly associated with a lower OS and a higher DSM (OS, $P < 0.001$, aHR = 2.377; DSM, $P < 0.001$, aHR = 2.04).

Discussion

This study delineated the distinct clinicopathological features of CRC in patients with different age groups. In contrast with young patients, older patients diagnosed with CRC were at significantly greater risk of OS and DSM. In addition, our analysis of metastases patterns demonstrated that the younger patients were more likely to diagnose liver metastasis than the older, whereas the older cases were less likely to appeared lung metastases compared to the younger.

In the current study, patients with age ≥ 65 were more likely to be female and white. The finding was consistent with previous population-based studies on sexes, showing that women presented at an older age [8]. This is somewhat in contrast to our reports that there were no differences in overall survival and cancer-related mortality between blacks and whites, and this may have resulted from identical treatment [9]. The racial differences we observed were likely a result of a complex interplay between screening access and uptake, and etiologic factors across different racial and ethnic populations. Available evidence suggested age and race at presentation accounted for a majority of CRC survival disparities, indicating that whites had the worst predicted Hazard ratio (HR) after age 75 and older CRC patients were significantly less likely to receive adjuvant chemotherapy than younger patients [10, 11]. Continued investigation is needed to fully understand the implications of the age-related survival disparities.

In this study, the colorectal cancers in old patients tended to be lower in grade, earlier in stage, smaller in size, have less lymph node and distant metastases, findings consistent with numerous published reports [5, 6, 12, 13]. However, it is possible that younger patients presented with later disease because they were not screened [14] or were at increased risk because of a higher prevalence of unhealthy life style or unknown environmental factors predisposing them to CRC. To explain on stage of disease and tumor grade, we had collect specific information on risk factors for developing CRC, such as having a family history of CRC, colorectal polyps, chronic inflammatory bowel disease, and history of genetic abnormalities [15-19]. Previous studies had documented that K-ras mutations were much less frequent in colonic tumors at younger ages, and the type of mutation was found to be associated to sex of patient and location of tumor [20, 21]. However, K-ras mutations were closely associated with patient prognosis can be landmarks of definitive therapeutic targets as well as useful biomarkers in CRC [22, 23]. Further, our results revealed that the older patients were more likely to primary derive from proximal colon, such as cecum, ascending, Hepatic Flexure and Transverse patterns. Previous studies of CRC had shown proximal colorectal cancers had a tendency to present at a more advanced stage and have a poorer prognosis [24-26]. Several studies also demonstrated that increasing age was the factor associated with a greater likelihood of developing CRC in a proximal location [27, 28]. Proximal colon cancers are more likely than rectal and distal colon tumors to have microsatellite instability, a CpG island methylator phenotype, and K-ras mutations, whereas rectal and distal colon tumors are more likely than proximal colon tumors to have a p53 mutation [29].

Our study had some limitations. We did not have information for this cohort regarding systemic treatments, such as surgery and chemotherapy, which might contribute to some of the differences observed in survival. In conclusion, we identified clear differences within age groups in both OS and DSM for CRC, which warrant further investigation. Future translational studies require prospective validation and should focus on the tumor biology and treatment efficacy of CRC. However, our study has laid a foundation for using the differences among age groups to develop and evaluate personalized therapies for CRC in clinical trials.

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Disclosure of conflict of interest

None.

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